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ESOPHAGEAL LESIONS ASSOCIATED WITH ACROSCLEROSIS AND SCLERODERMA

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The dermatoscleroses constitute a group of diseases in which changes of the connective tissues of the body are predominant. One of us (O'Leary [1]) has discussed four dermatologic entities: namely, scleroderma, acrosclerosis, scleredema and dermatomyositis, all of which have a certain degree of cutaneous sclerosis as part of the clinical picture. Fundamental disturbances of the connective tissues are involved in each of these syndromes. Scleroderma and acrosclerosis are alike in that sclerosing processes take place in the lower portion of the cutis. Acrosclerosis differs from scleroderma in that the trophic disorder in the former appears to have its origin in vasomotor disturbances. Acrosclerosis is a sclerodermic process which involves the distal parts of the extremities and the face and neck of patients who present the phenomena of Raynaud's disease. We believe that it constitutes a distinct clinical entity.

As Weiss and his associates [2] have pointed out, the changes of connective tissue in scleroderma are not confined to the integument. Disturbances of the heart, lungs and gastrointestinal tract have been described in association with scleroderma and allied conditions. Difficulties of deglutition frequently constitute a striking feature of the clinical picture. The oral lesions of scleroderma are well recognized, and the ingestion of food is often difficult because of them. Disturbances of the passage of food through the esophagus are recognized less frequently. It is our purpose to discuss the lesions of the esophagus that may accompany acrosclerosis and scleroderma. Cases of scleredema and dermatomyositis have been excluded from this study.

REVIEW OF THE LITERATURE

In 1903 Ehrmann [3] first recorded the occurrence of dysphagia in a case of acute scleroderma. He performed an esophagoscopic examination on the patient and noted changes of the esophageal wall. Since then 31 additional cases have been reported in some detail.[4] All available reports of cases have been studied. The essential facts derived from this review have been summarized in table 1.

TABLE 1.—*Summary of Data on Cases Reported in the Literature*

Total cases reported of scleroderma with esophageal lesions, 32. Sex: male 7, female 25.		
Dermatologic classification (when possible)		27
Acrosclerosis	21	
Scleroderma (generalized)	4	
Acute edematous scleroderma	1	
Localized scleroderma	1	
Roentgenologic features		24
Stenosis in lower part of esophagus	8	
Retardation, lack of motility	11	
Dilatation or cardiospasm	5	
Esophagoscopic features		8
Stenosis in lower part of esophagus	5	
Changes restricted to esophageal wall	3	
Cases in which necropsy was performed		8

The authors of previous articles on this subject were in general agreement that the esophageal disturbances associated with scleroderma are the result of the presence of sclerodermatous changes in the walls of the esophagus. The results of

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1. O'Leary, P. A.: Dermatosclerosis, Canad. M. A. J. **48**: 410-415 (May) 1943.

2. Weiss, S.; Stead, E. A., Jr.; Warren, J. V., and Bailey, O. T.: Scleroderma Heart Disease, with Consideration of Certain Other Visceral Manifestations of Scleroderma, Arch. Int. Med. **71**: 749-776 (June) 1943.

3. Ehrmann, S.: Ueber die Beziehung der Sklerodermie zu den autotoxischen Erythemen, Wien. med. Wchnschr. **53**: 1097-1156, 1903.

4. The four cases reported by Barasciutti (Barasciutti, A.: La disfagia degli sclerodermici; indagini radiologische e cliniche; rilievi patogenetici e terapeutici, Gior. di clin. med **18**: 885-899 [Oct. 10] 1937.) are not included, as the detailed report of cases has not been available for study.

examination at necropsy were described in 8 cases. Grossly, the esophagus usually was dilated, and the mucosa was thickened and had a varnished appearance. In the case reported by Rake [5] there was associated ulcerative esophagitis. In 1 of the cases of Weissenbach, Stewart and Hoesli [6] there was apparent leukoplakia in the lower part of the esophagus. In all the 8 cases, the microscopic observations were similar. The submucosa was thickened and infiltrated with round cells. Fragmentation of elastic fibers was demonstrated, and the muscular layer was atrophied. Perivascular infiltration was also characteristic. In other words, the histologic features were those of sclerosis of the connective tissues.

Roentgenographic studies of the esophagus were carried out in 24 of the cases reviewed in the literature. In 1916 Schmidt [7] made a roentgenoscopic examination of a patient suffering from scleroderma and dysphagia and observed the passage of barium sulfate. Although no lesion was detected in the esophagus, he found that fifteen minutes was required for passage of the barium into the stomach. Kuré and his associates [8] made rather elaborate roentgenologic studies of the esophagus in 5 cases of scleroderma. Three of the patients apparently did not have any difficulty in swallowing. Employing a modified barium meal, Kuré and his associates [9] recorded the time required for the passage of the meal from the mouth to the stomach, with the patient both in the upright position and in the dorsal decubitus position. After having established the time intervals for normal subjects, they found that the passage of the meal was retarded greatly for their patients suffering from scleroderma. The retardation was especially prolonged in the dorsal decubitus position. As might be expected, the greatest delay in passage was noted at the cardia. Weissenbach and his associates [10] made similar time studies in a case of dysphagia, using the technic of Kuré and his associates.[9a] In addition to the retardation of the bolus, they observed that the normal peristaltic movements were absent and that there were a gaping of the esophagus and a tendency for the barium meal to adhere to the walls of the esophagus. Lindsay and his associates [11] noted reduced peristalsis in 1 of their patients and absence of peristalsis in another.

Dilatation of the esophagus was described by roentgenographic means in the cases of Rake,[5] Nomland [12] and Jackman.[13] The passage of barium was retarded at the cardia in each of these cases. In Jackman's case the barium was retained above the cardia for eight hours. The clinical diagnosis was cardiospasm in each instance.

Stenosis of the lower part of the esophagus has been described in 8 cases by roentgenoscopic study. In 5 of these cases the roentgenologic findings were confirmed by esophagoscopic examination. In Dowling's [14] case the finding of a stricture in the middle segment of the esophagus was not confirmed when necropsy was performed. Fessler and Pohl [15] reported the first stenosing lesion in the lower part of the esophagus in 1932. Lindsay, Templeton and Rothman [11] reported 3 cases in which an obstructing lesion was noted in the lower part of the esophagus. One of their patients (their case 3) is included in our series (case 4), because the patient previously had been a patient

5. Rake, G.: On the Pathology and Pathogenesis of Scleroderma, Bull. Johns Hopkins Hosp. **48:** 212-227 (April) 1931.

6. Weissenbach, R. J.; Steward, W. M., and Hoesli, H.: Troubles fonctionnels et lésions de l'oesophage dans la sclérodermie, Ann. de dermat. et syph. **79:**81-99 (Feb.); 198-219 (March) 1938.

7. Schmidt, R.: Sklerodermie mit Dysphagie, Deutsche med. Wchnschr. **2:** 1023, 1916.

8. (*a*) Kuré, K.; Yamagata, K.; Tsukada, S., and Hiyoshi, J.: Passagestörung des Oesophagus bei Sklerodermie und Dystrophia musculorum progressiva, Klin. Wchnschr. **15:** 516-529 (April 11) 1936. (*b*) Tsukada, S.: Röntgenologische Studien über die Veränderungen der Speiseröhre bei progressiver Muskeldystrophie und Sklerodermie, Mitt. d. med. Gesellsch. zu Tokyo **47:** 1914 (Oct.) 1933.

9. (*a*) Hiyoshi, J.: Beiträge zur Kenntnis der funktionellen Veränderung des Ösophagus durch röntgenologische Untersuchungen bei progressiver Muskeldystrophie und bei Sklerodermie, Mitt. d. med. Gesellsch. zu Tokyo **51:**799-800 (Aug.) 1937. (*b*) Footnote 8.

10. Weissenbach, R. J.; Dechaume; Martineau; Stewart, W. M., and Hoesli, H.: Un cas de syndrome de Thibierge-Weissenbach (sclérodermie progressive et calcifications) avec lésions bucco-pharyngées et oesophagiennes accentuées ayant nécessité la gastrostomie, Bull. Soc. franç. de dermat. et syph. **44:** 1053-1060 (June 10) 1937. Weissenbach, R. J.; Martineau; Bouwens; Pizon, and di Matteo: Sclérodermie progressive; syndrome de Thibierge-Weissenbach; ulcère de jambe et calcification en molletières; troubles oesophagiens, ibid. **44:**2018-2024 (Dec.) 1937.

11. Lindsay, J. R.; Templeton, F. E., and Rothman, S.: Lesions of the Esophagus in Generalized Progressive Scleroderma, J. A. M. A. **123:** 745-750 (Nov. 20) 1943.

12. Nomland, R.: Sclerodactylia with Calcification, Arch. Dermat. & Syph. **21:** 322-323 (Feb.) 1930.

13. Jackman, J.: Roentgen Features of Scleroderma and Acrosclerosis, Radiology **40:**163-168 (Feb.) 1943.

14. Dowling, G. B.: Generalized Sclerodermia, Brit. J. Dermat. **52:** 242-256 (Aug.-Sept.) 1940.

15. Fessler, A., and Pohl, R.: Stenosierender Prozess des Ösophagus bei Sklerodermie, Dermat. Ztschr. **63:** 164-169 (Feb.) 1932.

at the Mayo Clinic. Weiss and his associates [2] reported 2 cases of scleroderma in which there was organic stenosis in the lower part of the esophagus. In 1 of these cases esophagoscopic examination was performed. They also mentioned 5 additional patients who had come under their observation and who had scleroderma and constricting lesions in the lower part of the esophagus.

In 8 of the cases reported in the literature esophagoscopic examination was performed, and, as noted previously, stenosis of the lower part of the esophagus was found in 5 of these cases. In the remaining 3 cases changes were noted in the lining of the esophagus. Ehrmann [3] noted thickening of the esophageal wall. Schwarz [16] described esophagitis. Lindsay, Templeton and Rothman [11] found inflammatory changes in the lower two thirds of the esophagus, with a diffuse white membrane in the lower part of the esophagus, about 4 or 5 cm. above the diaphragmatic level.

The dermatologic diagnosis in all of the 32 cases reported in the literature was scleroderma. No attempt was made to distinguish diffuse scleroderma from scleroderma occurring in association with Raynaud's syndrome (acrosclerosis). Twenty-seven of the reports of cases were presented in sufficient detail to enable one to classify the type of dermatosclerosis. In 21 of the cases vasomotor symptoms affecting the upper extremities had been noted prior to the onset of the cutaneous lesions. These cases may be classified as instances of acrosclerosis. Generalized scleroderma was apparently present in 4 cases, acute edematous scleroderma in 1 case and localized scleroderma in the remaining case.

An outstanding contribution to the study of the esophageal lesions of the sclerodermic diseases was made by Hoesli [17] in the thesis for his doctor's degree in 1937. Hoesli presented data on 3 cases which had been studied thoroughly and reviewed the literature in detail. Lindsay, Templeton and Rothman [11] have presented an excellent discussion of the subject, with the report of 5 cases. Weiss and his collaborators [2] have presented data on 2 cases of esophageal lesions in a paper that was concerned primarily with the cardiac manifestations of scleroderma. Recently Hale and Schatzki [18] reported a series of 22 cases of scleroderma in which there were roentgenologic changes attributable to the disease. In 13 of these cases there was evidence of retardation of the passage of barium through the lower part of the esophagus. Data on 4 of these cases were presented in detail. In 1939 Ochsner and DeBakey [19] called attention to the presence of esophageal obstruction in 1 of their cases of scleroderma.

ANALYSIS OF EXPERIENCE OF MAYO CLINIC

The records of all patients seen at the Mayo Clinic from 1930 to 1943, inclusive, for whom diagnoses of scleroderma or acrosclerosis had been made were reviewed. These records were studied with respect to the occurrence of esophageal symptoms or signs. In 36 of approximately 350 cases of scleroderma or acrosclerosis reviewed, dysphagia occurred or lesions of the esophagus were demonstrated (table 2). Roentgenographic studies were performed in 24 cases, and esophagoscopic examination was performed in 8 of these cases.

This study is concerned primarily with 18 cases in which conclusive roentgenographic or endoscopic observations were made. Reports

TABLE 2.—*Data Concerning Thirty-Six Cases of Acrosclerosis or Scleroderma in Which There Were Esophageal Signs or Symptoms*

I.	18 cases with positive roentgenographic or endoscopic observations
A.	Age distribution: 34 to 61 years
B.	Sex: female 13, male 5
C.	Dermatologic diagnosis: acrosclerosis, 18
D.	Roentgenologic diagnosis, 18 cases
1.	Esophageal dilatation or cardiospasm, 6
2.	Hiatal hernia, 9
3.	Negative results of examination, 3 *
E.	Esophagoscopic diagnosis, 8 cases
1.	Hiatal hernia (corroborated roentgen diagnosis), 5
2.	Sclerodermic involvement in patient with esophageal dilatation (by roentgen study), 1
3.	Sclerodermic involvement of esophageal wall not shown by roentgenologic examination, 2
F.	Passage of sounds, 7 cases
1.	Diagnosis and treatment of cardiospasm, 3
2.	Dilatation of stricture associated with hiatal hernia, 4
II.	6 cases with negative roentgenographic findings and no endoscopic studies
A.	Age distribution: 23 to 60 years (average 44)
B.	Sex: female 2, male 4
C.	Dermatologic diagnosis: acrosclerosis 4, scleroderma 2
III.	12 cases with neither roentgenographic nor endoscopic studies
A.	Age distribution: 17 to 66 years (average 35)
B.	Sex: female 9, male 3
C.	Dermatologic diagnosis: acrosclerosis 11, scleroderma (acute) 1

* In 2 of these cases esophagoscopic examination demonstrated changes in the esophageal wall. In the remaining case a diagnosis of cardiospasm was made by passage of sounds.

16. Schwarz, P.: Sklerodermie und Röntgenkastration, Schweiz. med. Wchnschr. **56**:246-248 (March) 1926.

17. Hoesli, H.: Troubles fonctionnels et lésions de l'oesophage dans la sclérodermie, Thesis, Paris, Jouve & Cie, 1937.

18. Hale, C. H., and Schatzki, R.: The Roentgenological Appearance of the Gastrointestinal Tract in Scleroderma, Am. J. Roentgenol. **51**:407-420 (April) 1944.

19. Ochsner, A., and DeBakey, M.: Scleroderma; Symposium; Surgical Considerations, New Orleans M. & S. J. **92**: 24-30 (July) 1939.

of these 18 cases are presented briefly. The symptoms of Raynaud's syndrome preceded or were coincident with the development of cutaneous manifestations in all 18 cases. In all these cases the diagnosis was acrosclerosis. Table 3

TABLE 3.—*Patients Who Had Dysphagia but Negative Roentgenographic Examination and with No Endoscopic Studies*

Age, Years	Sex	Dermatologic Diagnosis
45	F	Acrosclerosis
55	M	Acrosclerosis
40	M	Scleroderma *
60	M	Scleroderma
23	M	Acrosclerosis
39	F	Acrosclerosis

* This case was reported by Pugh, Kvale and Margulies (Proc. Staff Meet., Mayo Clin. **20**: 410 [Oct. 31] 1945). Changes in the intestine which were characteristic of scleroderma were recognized by roentgenoscopic examination.

presents data for 6 patients who complained of dysphagia but for whom the results of roentgenographic studies were inconclusive and for whom no endoscopic studies were made. Twelve patients had dysphagia, but no roentgenographic or endoscopic studies were made (table 4).

TABLE 4.—*Patients Who Had Dysphagia But No Roentgenographic or Endoscopic Studies*

Age, Years	Sex	Dermatologic Diagnosis
18	F	Acrosclerosis
31	F	Acrosclerosis
40	F	Acrosclerosis
31	F	Acrosclerosis
40	F	Acrosclerosis
37	F	Acrosclerosis
32	F	Acrosclerosis
35	M	Acrosclerosis
38	M	Acrosclerosis
66	F	Scleroderma (acute)
41	M	Acrosclerosis
17	F	Acrosclerosis

Roentgenographic Observations.—Conclusive roentgenographic features were demonstrated in 15 cases. Esophageal dilatation with atony of the esophageal musculature was noted in 6 instances (cases 8, 9, 10, 11, 12 and 18). Peristaltic movements were decreased or absent in these cases. Apparent spasm at the cardia, with obstruction, was noted in 4 of the 6 cases (cases 9, 10, 11 and 12), and the passage of the barium meal was slower than normal in these cases. No studies were made of this group in the dorsal decubitus position. A roentgenoscopic diagnosis of cardiospasm was made in these cases.

In 9 cases (cases 1, 2, 3, 4, 5, 6, 7, 16 and 17) a diagnosis of esophageal hiatal hernia was made. In these cases part of the stomach was found to be above the level of the diaphragmatic hiatus. The herniated portion of the stomach was distinguished readily from the phrenic ampulla of the esophagus. The patients were studied roentgenoscopically in both the upright position and the dorsal decubitus position. The passage of barium through the esophagus was slower than normal in each instance. In 2 of the cases (cases 3 and 5) there was obvious dilatation of the esophagus, giving the appearance of associated cardiospasm. In 6 of these 9 cases (cases 1, 2, 3, 4, 16 and 17) the hernia was definitely of the short esophagus type, and there was an associated stricture of the lower part of the esophagus and esophagogastric junction.

Roentgenographic studies were made in an additional 9 cases, but results were reported as negative. No attempt was made to study these 9 patients in the dorsal decubitus position or to carry out the elaborate time studies advised by Kuré and his associates.[8a] It is probable that the time required for the passage of barium would have been found to be prolonged if Kuré's technic had been used.

Endoscopic Observations. — Esophagoscopic examination was performed in 8 cases. In 5 of these cases, a previous diagnosis of esophageal hiatal hernia had been made by roentgenographic means. The diagnosis of hiatal hernia was confirmed in each instance. Strictures were observed in 2 cases (cases 2 and 3) in association with hernias of the short esophagus type. The obstructions in both cases appeared to be the result of inflammation. In 2 other cases (cases 4 and 5), ulceration was noted at the esophagogastric junction. In 1 case (case 6) no ulceration was seen. In all these cases the gastric mucosa of the hernia could be visualized. Specimens were removed for biopsy in 3 of these 5 cases (cases 2, 3 and 4)—that is, in the 2 cases in which there were strictures and in 1 case in which there was severe ulceration of the lower part of the esophagus. The tissues removed disclosed inflammatory changes so great that it was not possible to detect sclerodermatous changes. In one of the strictures definite gastric mucous membrane could be demonstrated (case 3).

In 1 case (case 18) in which diffuse dilatation of the esophagus without obstruction at the cardia was described roentgenographically, the esophagoscopic picture was that of severe atrophic esophagitis. In the remaining 2 cases in which esophagoscopic examination was performed, roentgenography had shown nothing abnormal. The evidence in 1 case was minimal (case 15): The mucosa was pale and smooth but otherwise normal. In the other case (case 14) there were severe induration and thickening of the wall of the upper part of the esophagus. The changes appeared to be due to a sclerodermatous process.

Esophagoscopic examination of patients who have scleroderma is often extremely difficult. If general anesthesia is employed, the procedure is much less formidable than in other circumstances. Pentothal sodium administered intravenously provides satisfactory anesthesia. This drug was used in almost all the cases in our series in which esophagoscopic examination was performed.

Passage of Esophageal Sounds.—In 7 of the 18 cases in which roentgenographic or endoscopic evidence was conclusive, esophageal sounds were passed over previously swallowed threads. Considerable information concerning the nature of the obstructing lesions in the esophagus can be obtained from the passage of sounds. In 1 case (case 13) a diagnosis was made of cardiospasm even though roentgenographic studies failed to reveal any obstruction at the cardia. Dilatation was performed for cardiospasm in 3 cases (cases 9, 10 and 13) and for relief of dysphagia due to the stricture associated with short esophagus in another 4 cases (cases 1, 2, 3 and 16). Relief or partial relief was obtained in all these cases, although recurrence of dysphagia at a later date was fairly common.

Symptomatology.—In 34 of the 36 cases under consideration a history of dysphagia could be obtained. Most frequently the sense of obstruction was localized by the patient to the lower part of the esophagus. A few patients complained of a sense of a lump in the upper part of the esophagus or even in the hypopharynx. Those patients whose difficulty in swallowing consisted in difficulty in getting the food off the back of the tongue because of fixation of the oral structures were excluded from this series. In some cases the difficulty in swallowing was intermittent. In other cases the dysphagia was constant and progressive. Variations of the degree of dysphagia frequently suggested that esophageal spasm was superimposed on an organic obstruction.

Pain and burning on swallowing occurred in some cases. More commonly patients complained of substernal burning an hour or more after eating or especially when they would lie down. Frequently this distress was accompanied with epigastric pain, often extending to the back. Sometimes these symptoms were relieved by the ingestion of sodium bicarbonate or other antacid preparations.

The vasomotor phenomena associated with acrosclerosis almost invariably preceded the esophageal symptoms. In most instances the sclerodermatous changes also preceded the dysphagia or substernal burning. Rarely the esophageal disturbance was responsible for the symptom of which the patient complained primarily (cases 3, 4 and 18). Actually the esophageal disturbance was most often a delayed manifestation of the disease. This observation is in accordance with those of Hoesli,[17] who reviewed all reported instances of esophageal disturbance in association with scleroderma up to 1937.

Prognosis.—As O'Leary and Waisman [20] have pointed out, the prognosis of acrosclerosis is considerably more favorable than that of diffuse scleroderma. Many of these patients had had vasomotor symptoms for some years prior to the onset of cutaneous lesions. Esophageal lesions tend to occur in cases of advanced acrosclerosis. The occurrence of esophageal difficulties is often a bad prognostic sign. However, in some of our cases (cases 1, 2, 5, 7 and 13) there was definite evidence that the dermatologic process had been arrested. Diffuse scleroderma is almost invariably progressive. The prognosis of the esophageal lesion is usually determined by the progress of the primary disease. In many cases acrosclerosis appears to be self limited. In these cases the esophageal symptoms are not difficult to control.

Treatment.—It is not the province of this report to discuss the treatment of acrosclerosis or scleroderma. However, the treatment of the esophageal lesion does merit consideration. When the esophageal difficulties are obstructive, temporary relief can be obtained almost invariably by dilatation of the esophagus with sounds over a previously swallowed thread. This method of treatment has been used both in the group of cases in which there was spasm at the cardia and in that in which there was stricture of the lower part of the esophagus associated with short esophagus and intrathoracic stomach. The 41 and 50 French sounds are used to dilate the cardia in those cases in which there is cardiospasm. In cases of cardiospasm associated with acrosclerosis or scleroderma, hydrostatic dilatation is not advisable. Sometimes the passage of the esophagoscope alone is enough to relieve the dysphagia of patients suffering from acrosclerosis (cases 5, 6 and 14). The selection of sounds for use in dilating the esophageal strictures depends on the degree of obstruction and the firmness of the lesion. Usually 29, 37 and 45 French sounds may be passed successively in these cases. It is not advisable to use sounds

20. O'Leary, P. A., and Waisman, M.: Acrosclerosis, Arch. Dermat. & Syph. **47**: 382-397 (March) 1943.

larger than the 45 French sound in dilating organic lesions of the esophagus.

Frequently, repeated passage of sounds is necessary to maintain an adequate esophageal lumen. In 1 of our cases (case 1) in which the esophagus was shortened and a stricture was present, dilation was performed on thirty-two occasions from 1926 to 1941, inclusive. Frequent dilation was necessary in the early stages. However, the intervals have become progressively longer and in recent years the patient has had little difficulty in swallowing.

COMMENT

In this study it was apparent that esophageal disturbances occur almost exclusively in cases of acrosclerosis rather than in those of generalized or diffuse scleroderma. It is not our purpose to discuss here the dermatologic differential diagnosis between these syndromes. However, it should be pointed out that the cutaneous lesions of acrosclerosis are confined to the hands, forearms, neck and upper part of the thorax, while diffuse scleroderma may involve the entire skin or the trunk, arms and hands. The facial lesions of acrosclerosis are likely to involve the oral cavity and to spread to the esophagus. When esophageal lesions are encountered in diffuse scleroderma, it is usually in those rare cases in which the scleroderma is cephalic in origin. Hence esophageal lesions are likely to occur in those cases in which there is early involvement of the face.

The constant association of Raynaud's phenomena with acrosclerosis suggests that a disturbance of the autonomic nervous system may be involved in the pathogenesis of acrosclerosis. Inasmuch as an imbalance between parasympathetic and sympathetic innervation is reputed to be a factor in the production of cardiospasm and other functional disturbances of the esophagus, it may be inferred that some common etiologic factor exists for the vasomotor, dermatologic and esophageal disturbances observed in acrosclerosis. Unquestionably, visible alterations of the lining of the esophagus have been demonstrated in the course of necropsy as well as at esophagoscopic examination in many of the cases of acrosclerosis. These changes are comparable both grossly and microscopically to those observed in the skin. However, there have been a considerable number of cases in which the esophageal lining appeared normal or nearly normal. It is postulated, therefore, that both organic changes in the walls of the esophagus and disturbances of its innervation may be involved in the disturbed function of the esophagus.

Obstruction to the passage of food is the most common esophageal symptom of which patients suffering from acrosclerosis complain. It is apparent from the records that these patients may have either organic lesions in the esophagus or disturbances of function. As has been pointed out by Kuré,[21] by Weissenbach [22] and by Lindsay,[11] and their respective associates, disturbances of the motility of the esophagus may be demonstrated fairly early in the course of the disease. By the aid of a stop watch, delay of the passage of barium may be detected before the patient complains of dysphagia. The next change that is observed is a decrease or absence of the normal peristaltic movements of the esophagus. Normally the muscular activity of the esophageal wall is responsible for the rapid passage of food into the stomach. The peristaltic movements normally propel the food through the esophagus, and the cardiac sphincter opens in response to peristaltic waves. In the absence of muscular activity in the esophagus, gravity causes the food to pass slowly into the stomach. The greatest obstruction is at the cardiac sphincter, because there has not been any peristaltic wave to inhibit its action. In cases of more advanced acrosclerosis, gaping and ultimately dilatation of the esophagus take place.

Cardiospasm or achalasia of the esophagus may be defined as a dilatation of the esophagus in association with a nonorganic obstruction at the cardia. Cardiospasm is primarily a disturbance of the function of the esophageal musculature. This dysfunction is probably due to an imbalance of the autonomic innervation of the esophagus. The explanation for the functional esophageal disturbances in acrosclerosis is similar to that of cardiospasm except for the fact that in at least some instances sclerodermic changes in the esophageal wall are responsible for inadequate muscular activity. In other cases of acrosclerosis changes in the esophageal wall are not demonstrable, and it is possible that disturbances of the autonomic nervous system are a factor in such cases. The occurrence of esophageal troubles after the onset of the vasomotor disturbances in the upper extremities and sometimes either before or coincident with cutaneous

21. Kuré, K., and Hiyoshi, J.: Sklerodermie mit Muskeldystrophie, Ztschr. f. d. ges. Neurol. u. Psychiat. **156:** 36-44, 1936. Kuré, Yamagata, Tsukada and Hiyoshi.[8a]

22. Weissenbach, R. J.; Stewart, W., and Hoesli, H.: Les troubles fonctionnels oesophagiens et les lésions de l'oesophage dans la sclérodermie, Bull. Soc. franç. de dermat. et syph. **44:** 1060-1063 (June 10) 1937.

lesions suggests that the origin of the entire syndrome possibly may be in the autonomic nervous system.

The occurrence of hiatal hernia in association with acrosclerosis is more difficult to explain than that of cardiospasm. The characteristic "hidebound" appearance of patients suffering from acrosclerosis and scleroderma is due to the contraction of the skin over the affected parts. When sclerosis takes place in the connective tissue of the esophageal wall it is probable that there is an actual shortening of the esophagus. The cardiac portion of the stomach is pulled up into the thorax through the hiatus of the diaphragm. The typical appearance of short esophagus with hiatal hernia may be produced.

At this point it is desirable to discuss briefly shortening of the esophagus as it occurs in persons who are otherwise normal. The roentgenographic appearance of hiatal hernia of the short esophagus type is characteristic. The lower part of the esophagus lacks redundancy. The anterior and left lateral angulation of the esophagus just above the diaphragmatic hiatus is absent. The herniated portion of the stomach above the diaphragm appears as a pouch, which sometimes is confused with the phrenic ampulla of the esophagus. In some instances the characteristic pattern of the gastric mucosa may be discerned on roentgenoscopic examination. At esophagoscopic examination the lower part of the esophagus is observed to be a straight tube. There is gaping of the lowermost portion of the esophagus, and the usual tonic closure between esophagus and stomach is absent. The dark red appearance of the gastric mucosa stands out in sharp contrast to that of the pale esophageal mucosa. If necessary, tissue may be taken from the esophagogastric junction in order to demonstrate conclusively that the gastric mucous membrane is present above the diaphragmatic hiatus.

With hiatal hernia of the short esophagus type, the sphincteric property of the cardia is no longer present. When the patient is in the recumbent position, gastric secretions freely regurgitate into the esophagus. The esophageal lining is unable to resist the digestive action of the gastric acids and enzymes. Inflammation and ulceration take place in the lower part of the esophagus. The patient often complains of substernal burning, especially when lying down. Alternate ulceration and healing in the lower part of the esophagus often result in strictures of this segment of the esophagus and of the esophagogastric junction. Actual ulceration in the hernial sac is much less common than in the esophagus. When ulceration is present in the herniated gastric mucosa, it is usually traumatic in origin.

The organic stenosis that occurs with short esophagus is confused frequently with carcinoma of the lower part of the esophagus and with cicatricial stricture of the esophagus due to other causes. It must be borne in mind that repeated ulceration and scarring of the lower part of the esophagus result in progressive shortening of the esophagus. We are in agreement with Allison and his associates,[23] who have stated their belief that short esophagus is more often acquired than congenital in origin.

The foregoing considerations are applicable to all hiatal hernias of the short esophagus type, including those that occur in association with acrosclerosis. In this series, a roentgenologic diagnosis of hiatal hernia was confirmed in 5 cases by esophagoscopic examination. Gastric mucosa was identified readily above the diaphragmatic "pinchcock" in each case, and in 1 instance biopsy of tissue from the esophagogastric junction clearly revealed gastric mucosa. In 2 other instances biopsy was performed on tissue from regions denuded of mucosa in order to exclude neoplastic disease. The 5 cases illustrate the several stages of development; namely, simple hiatal hernia, hernia with ulceration of the esophagogastric junction and hernia with stricture of the lower part of the esophagus. One of our patients was observed at a later stage by Lindsay and his associates. At the time of our examination a hiatal hernia associated with severe ulceration was found, but no stenosis had occurred. When this patient was examined by Lindsay and his associates, they described a moderate degree of stenosis. Although Lindsay and his associates interpreted this lesion as a stricture of the esophagus above the phrenic ampulla, they did state that the mucosa below the stricture was darker than that of the esophagus and that the color approximated that of gastric mucosa.

It is of interest that in 2 of our cases the roentgenologist described the feature of cardiospasm in addition to those of hiatal hernia with intrathoracic stomach. The absence of normal muscular activity, the esophageal dilatation, the abnormal behavior of the cardiac sphincter and the shortening of the esophagus must all contribute to the esophageal disturbance. The sclerosis of the connective tissues of the esophagus must be considered the basic factor in the causation of the esophageal symptoms and signs.

23. Allison, P. R.; Johnstone, A. S., and Royce, G. B.: Short Esophagus with Simple Peptic Ulceration, J. Thoracic Surg. **12**:432-457 (June) 1943.

Disturbances of the innervation of the esophageal musculature also may play an important part. The development of hiatal hernia associated with peptic ulceration of the lower part of the esophagus and resultant stenosis appears to be a secondary process.

REPORT OF CASES

CASE 1.—The patient, a single woman aged 48, registered at the clinic on June 16, 1922. Her vasomotor symptoms had begun in 1909, but her cutaneous lesions, which involved her hands, feet and face, had not begun until 1918.

A dermatologic diagnosis of acrosclerosis was made. On roentgenographic examination it was evident that the esophagus was shorter than normal and that there were a hiatal hernia and a stricture at the esophagogastric junction. Esophagoscopic examination was not performed.

At the patient's first visit to the clinic her condition was recognized as a vasomotor type of scleroderma. Her esophageal symptoms began in 1923. Dysphagia consisted in obstruction to passage of food in the lower part of the substernal region. On thirty-two occasions from 1926 to 1941, inclusive, the stricture was dilated, the largest sound used being a 45 French sound. The dysphagia always was relieved by dilation, and as the years have passed the intervals between dilations have become increasingly longer. Bilateral cervicothoracic ganglionectomy was performed in June 1929. There was improvement after the operation, and scleroderma has not progressed.

CASE 2.—The patient, a married woman aged 48, registered at the clinic on Nov. 25, 1942. Her vasomotor symptoms had begun in 1919; her cutaneous lesions, which involved her hands, feet and face, probably had begun in 1941, and her esophageal symptoms had begun in March 1942.

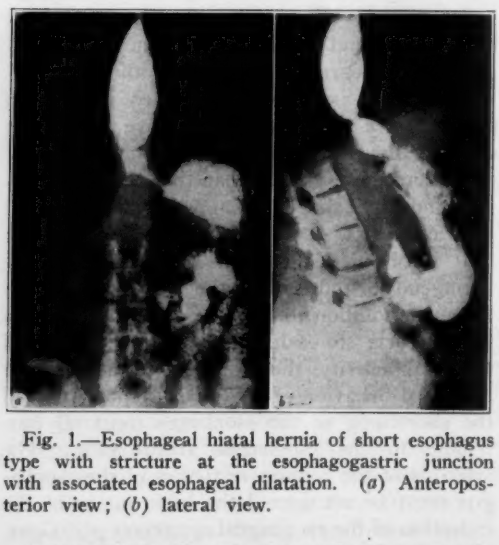

Fig. 1.—Esophageal hiatal hernia of short esophagus type with stricture at the esophagogastric junction with associated esophageal dilatation. (*a*) Anteroposterior view; (*b*) lateral view.

A dermatologic diagnosis of acrosclerosis was made. On roentgenographic examination it was evident that the esophagus was shorter than normal and that there were a hiatal hernia and a stricture at the esophagogastric junction. The esophagoscopic examination likewise showed a short esophagus with intrathoracic stomach and a stricture at the esophagogastric junction. At biopsy of tissue from the esophagogastric junction the tissue was observed to have been the site of inflammation.

The stricture was dilated, the largest sound used being a 45 French sound.

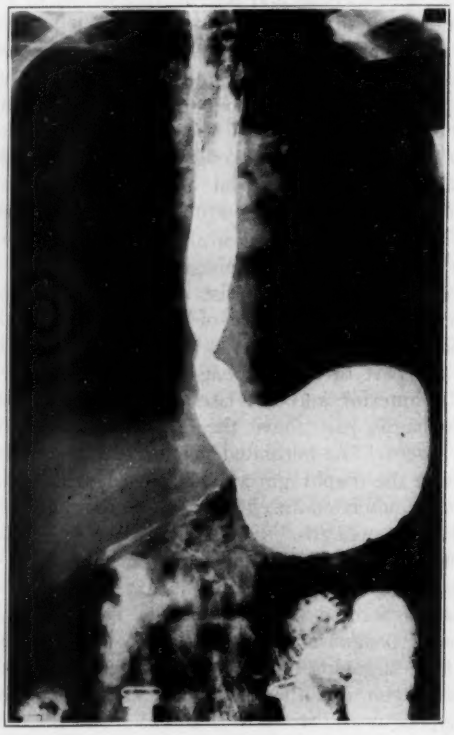

Fig. 2.—Hiatal hernia of the short esophagus type with about 2 inches (5 cm.) of the stomach above the diaphragm. At esophagoscopic examination severe ulceration of the lower part of the esophagus and at the esophagogastric junction was observed. There was no dysphagia at the time of our examination. This patient was examined some time later by Dr. Lindsay (Lindsay, Templeton and Rothman,[11] case 3). By this time a definite stricture had formed.

In this case there was a history of Raynaud's disease over a long period. The cutaneous changes had been recent and insidious in their onset. Dysphagia had been present for nine months when the patient came to the clinic. Dilation relieved the dysphagia. Bilateral cervicothoracic ganglionectomy was performed at the clinic. The patient returned for a recheck Aug. 10, 1943. At that time her condition was definitely improved, and there was no dysphagia.

CASE 3.—The patient, a married woman aged 61, registered at the clinic May 25, 1942. The vasomotor symptoms and the cutaneous lesions, which involved the hands, arms, face and thorax, had begun, apparently simultaneously, in 1938, but the esophageal symptoms, of which the patient complained primarily, had not begun until the autumn of 1939. Food had seemed to

stick in the lower part of the substernal region. Dilation of the esophagus had given relief.

A dermatologic diagnosis of acrosclerosis was made. Roentgenographic examination showed cardiospasm with 1 inch (2.5 cm.) of stomach above the diaphragm (fig. 1). On esophagoscopic examination it was observed that there was esophageal hiatal hernia with secondary stricture at the esophagogastric junction. The mucosa was thin, and there were induration and fixation of the esophageal wall. The mucous membrane below the stricture was of the gastric type. On biopsy of a specimen of gastric mucous membrane, the tissue was observed to have been the site of inflammation.

The stricture was dilated on May 28, 1942 and on April 21, 1943, the largest sound used at each dilation being a 45 French sound. Dysphagia improved after each dilation. In November 1943, the patient's physician wrote that she was having trouble with her feet, with ulcers about the ankles.

CASE 4 (reported by Lindsay, Templeton and Rothman as their case 3).—The patient, a man aged 46, registered at the clinic on July 27, 1942. His illness had begun in October 1940, with pain in the epigastrium and the lower part of the substernal region, chiefly at night. This was the symptom of which the patient complained primarily. The syndrome was typical of hiatal hernia. There was no dysphagia. The vasomotor symptoms had begun in January 1941, and the cutaneous lesions, which involved the hands, arms, abdomen and face, had begun in September of the same year. In other words, Raynaud's phenomena had preceded the cutaneous lesions.

A dermatologic diagnosis of acrosclerosis was made. On roentgenographic examination an esophageal hiatal hernia, with about 2 inches (5 cm.) of stomach above the diaphragm, was observed. Otherwise, the stomach was normal (fig. 2). Esophagoscopy revealed a hiatal hernia, with severe ulceration and erosion at the esophagogastric junction and in the hernial sac itself. Biopsy of removed tissue disclosed that the tissue had been the site of inflammation. Since there was no dysphagia, dilation was not performed.

CASE 5.—The patient, a single woman aged 41, registered at the clinic on Aug. 12, 1935. Her vasomotor symptoms had begun in 1929, and her cutaneous lesions, which involved her hands, feet and face, had begun in 1931. The esophageal symptoms had not begun at the time of her first registration. A dermatologic diagnosis of acrosclerosis was made. The condition, primarily Raynaud's syndrome followed by thickening of the skin, was more or less stationary from 1935 to 1943.

In August 1940, esophageal symptoms began. Dysphagia was intermittent and was suggestive of spasm. At times there was subxiphoid pain on swallowing. On roentgenographic examination in 1941, hiatal hernia with a small segment of the stomach above the diaphragm was observed. There was some indication of cardiospasm, but this was doubtful. Esophagoscopy disclosed a small hiatal hernia and ulceration at the esophagogastric junction.

Dilation was not performed. The esophageal symptoms were relieved entirely by the passage of the esophagoscope in 1941. The patient has not had any trouble since.

CASE 6.—The patient, a married woman aged 62 years, registered at the clinic on Sept. 14, 1943. Her vasomotor symptoms had begun in 1926, and her cutaneous lesions, which involved her hands, face and feet, had begun in 1933. In other words, a typical Raynaud syndrome had preceded cutaneous involvement by several years. Esophageal symptoms had begun in 1939. They consisted in epigastric and substernal burning pain, symptoms typical of hiatal hernia. Nocturnal pain referred to the thoracic segment of the spinal column waked the patient from sleep. There was slight dysphagia at times.

A dermatologic diagnosis of acrosclerosis was made. Roentgenographic examination revealed an esophageal hiatal hernia with about 1 inch (2.5 cm.) of stomach above the diaphragm. On esophagoscopic examination a small hiatal hernia was observed, but there was no ulceration. Dilation was not done.

CASE 7.—The patient, a married woman aged 50, registered at the clinic on Nov. 24, 1936. Raynaud's phenomena and dysphagia had begun in 1914 at about the same time. The dysphagia had been progressive,

Fig. 3.—Diffuse dilatation of the lower half of the esophagus. This suggests cardiospasm, but no definite obstruction at the cardia was demonstrated.

and the patient was able to swallow only liquids when she came to the clinic. The onset of the cutaneous lesions, which involved the hands and perhaps the face, was insidious and occurred about 1926. For nine years before her admission to the clinic the patient had had deposits of calcium in her finger tips and toes.

A dermatologic diagnosis of acrosclerosis was made. On roentgenologic examination a short esophagus with intrathoracic stomach and stricture at the esophagogastric junction was observed. Esophagoscopic examination was not done.

Bilateral thoracic sympathectomy was performed. The patient's dysphagia improved postoperatively, and therefore dilation was not done. According to letters of 1941, the results of sympathectomy were good.

CASE 8.—The patient, a single woman aged 45, registered at the clinic on Oct. 1, 1940. The vasomotor symptoms and the cutaneous lesions, which involved the hands, face and mouth, had begun at about the same time in 1929 or 1930. The patient had never had much dysphagia, but she had had substernal burning for years. The onset of this had been about 1930.

A dermatologic diagnosis of acrosclerosis was made. Roentgenographic examination disclosed diffuse dilatation of the lower half of the esophagus, which suggested cardiospasm, but no definite obstruction was observed (fig. 3). Neither esophagoscopic examination nor dilation was done. No treatment was advised.

CASE 9.—The patient, a man aged 40, registered at the clinic on July 16, 1941. Vasomotor symptoms had begun in 1938. Sensitivity to cold had developed a few months before the cutaneous lesions appeared in 1939. The latter involved the hands, face, neck, thorax and back. Scleroderma had advanced rapidly, and when the patient was seen at the clinic it was more or less generalized The patient's condition was poor. Dysphagia, consisting of a sense of obstruction in the lower part of the substernal region and also at the cricoid level, had begun in 1940.

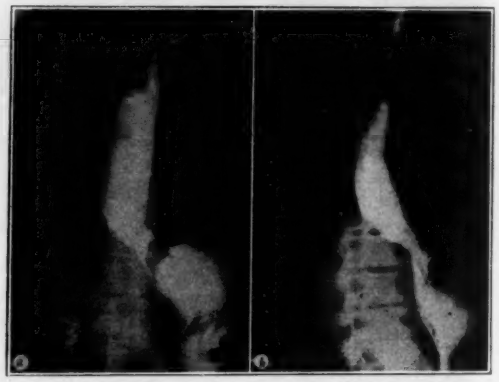

Fig. 4.—Cardiospasm with moderate dilatation of the esophagus in a case of acrosclerosis. (*a*) Anteroposterior view; (*b*) oblique view.

A dermatologic diagnosis of acrosclerosis was made. On roentgenographic examination cardiospasm with slight dilatation of the esophagus was observed. Esophagoscopic examination was not done.

Dilation relieved the dysphagia. The largest sound passed was a 50 French sound.

CASE 10.—The patient, a man aged 55, registered at the clinic on July 3, 1943. His vasomotor symptoms had begun in 1929, and his cutaneous lesions, which involved his hands, feet, face, mouth and lips, had begun about 1931. Bilateral cervicothoracic ganglionectomy had been performed in July 1933. Esophageal symptoms had begun in 1936. There was obstruction to passage of food at the cardia. In 1937 roentgenographic examination had showed slight cardiospasm. In the same year dilatation to a 60 French sound had relieved the obstruction, but there was a slight recurrence of obstruction in 1943.

A dermatologic diagnosis of acrosclerosis was made. When the patient was seen in August 1943, there was evidence of slight progression, especially in the face and mouth. Calcinosis of the fingers had devloped. Roentgenographic examination showed cardiospasm with moderate dilatation of the esophagus (fig. 4). Esophagoscopic examination was not done.

CASE 11.—The patient, a married woman aged 47, registered at the clinic on Oct. 31, 1938. Vasomotor symptoms had begun in 1913, but cutaneous lesions had not begun until 1933. The latter, which involved the fingers, toes, face, shoulders and thorax, were slowly progressive. Rather vague dysphagia had begun about 1936.

A dermatologic diagnosis of acrosclerosis was made. Roentgenographic examination gave evidence of cardiospasm. Neither esophagoscopic examination nor dilation was performed. From subsequent correspondence there was not much change of the patient's status. In this case the condition was advanced.

CASE 12.—The patient, a married woman aged 42, registered at the clinic on Aug. 18, 1937. The vasomotor symptoms, a typical Raynaud syndrome, had begun in 1932. The cutaneous lesions, involving the hands, face and thorax, had begun in 1936. The skin of fingers and face became tightened.

A dermatologic diagnosis of acrosclerosis was made. Bilateral cervicothoracic ganglionectomy was performed, but the results were not good. About 1940 esophageal symptoms began. The patient described recurring episodes of obstruction to passage of food in the lower part of the esophagus. Roentgenographic examination in 1941 showed evidence of cardiospasm. In 1944 dilation was performed on two occasions to relieve dysphagia. Good results were obtained.

CASE 13.—The patient, a married woman aged 61, registered at the clinic on June 6, 1933. Typical Raynaud's phenomena had begun in 1913. There had been ulceration of the finger tips and progression to the feet. The cutaneous lesions, which involved the hands, forearms, face, neck and feet, had begun in 1928. Dysphagia had begun at the same time as the cutaneous lesions, but it was intermittent. Food stuck above the cardia. The attacks of dysphagia came on suddenly, and sometimes complete obstruction persisted for twenty-four hours. The patient could feel the cardia open and food drop through.

A dermatologic diagnosis of acrosclerosis was made. On roentgenographic examination it was observed that the esophagus was normal but that a duodenal ulcer was present. Esophagoscopic examination was not performed. Dilation revealed and relieved spastic obstruction at the cardia. The largest sound passed was a 41 French sound.

The latest letter from the patient, dated 1935, two years after dilation, stated that the dysphagia had recurred but that the cutaneous lesions were stationary.

CASE 14.—The patient, a married woman aged 44, registered at the clinic on Dec. 9, 1942. Raynaud's phenomena had begun in October 1941, and cutaneous lesions, involving the hands, feet, face and thorax, had begun in May 1942. Esophageal symptoms had begun in July 1942. Pain and a sense of obstruction in the upper part of the esophagus were present on swallowing.

A dermatologic diagnosis of acrosclerosis was made. Roentgenographic examination showed that the esophagus and stomach were normal. On esophagoscopic examination thickening of the mucosa of the upper part of the esophagus and loss of elasticity of the esophageal wall were observed. These were interpreted as sclerodermic changes. Apparently there was some relief of the esophageal symptoms after passage of the esophagoscope, but subsequent progress has not been favorable.

CASE 15.—The patient, a man aged 48, registered at the clinic on June 8, 1933. Typical Raynaud's phenomena of the hands had begun in October 1928, and their onset had been followed by sclerodermic changes of the hands in April 1929. Ulceration of the finger tips occurred. Later the sclerodermic changes had involved the face, feet and toes. Dysphagia, consisting of a sense of tightness in the throat, making swallowing difficult, had begun in 1930. Bilateral cervical sympathectomy in 1931 had produced temporary relief.

A dermatologic diagnosis of acrosclerosis was made. On roentgenographic examination a normal esophagus and stomach were observed. Esophagoscopy showed pallor of the mucous membrane but no changes of motility. Dilation was not done. Bilateral cervicothoracic ganglionectomy produced relief of the cutaneous symptoms for only a few months. The patient died in July 1935.

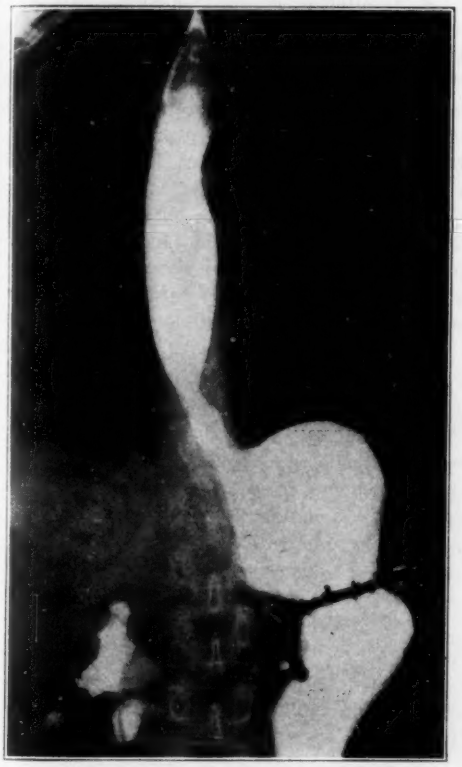

Fig. 5.—Short esophagus with hiatal hernia and stricture at the esophagogastric junction in a case of acrosclerosis.

CASE 16.—The patient, a married women aged 39, registered at the clinic on May 15, 1944. Vasomotor symptoms had developed in 1939, and cutaneous lesions, which involved the hands, face and feet, had developed in the following year. Since 1941 there had been progressive dysphagia with obstruction to the passage of food in the lower part of the esophagus. The patient's diet had been restricted to fluids for three months prior to registration.

A dermatologic diagnosis of advanced acrosclerosis was made. On roentgenographic examination an esophageal hiatal hernia of the short esophagus type, with about 2 inches (5 cm.) of stomach above the diaphragm, was observed (fig. 5). There was definite narrowing at the esophagogastric junction. There appeared to be associated spasm at the cardia. The pronounced thickening and rigidity of the mucosa of the esophageal entroitus prevented a satisfactory esophagoscopic examination. Dilation was performed over a previously swallowed thread, and the stricture was dilated to a 43 French sound. Striking relief from dysphagia was obtained.

CASE 17.—The patient, a married women aged 34, registered at the clinic on Jan. 21, 1941. In 1934 she had noted tingling and numbness in the fingers. In the ensuing few months cutaneous lesions had developed on hands, shoulders, neck and face. In 1936 deformities of the hands had appeared, and the sclerodermatous process had become more generalized. The dermatologic diagnosis was acrosclerosis with beginning involution and deposits of calcium in the finger tips.

There was no dysphagia at the time of the patient's first visit in 1941. Difficulty in swallowing developed within the next year and was rapidly progressive. Laparotomy was carried out elsewhere in 1942, and retrograde dilation of a stricture at the cardia was performed. This procedure was effective in relieving the dysphagia, and the patient has had little difficulty in swallowing since that time. When she returned to the clinic in 1944 severe destruction of the phalanges of both hands had occurred. Roentgenographic studies revealed a short esophagus with a short intrathoracic segment of stomach and narrowing at the esophagogastric junction. No peristaltic movements of the esophageal wall were noted.

CASE 18.—The patient, a man aged 56, registered at the clinic on Sept. 22, 1944. His vasomotor symptoms had begun in the spring of 1943, when he first noted pain and pallor of his hands and arms on exposure to cold. At the onset of his trouble swelling of his hands developed, but this symptom disappeared in the course of several months. He then noted stiffness in the skin of the face, neck and upper extremities. Dysphagia had been noted in May 1944, and this had been progressive.

A dermatologic diagnosis of acrosclerosis was made. Roentgenoscopic examination of the esophagus revealed diffuse dilatation with absence of peristaltic movements. No obstruction was detected at the cardia. Esophagoscopic examination was performed. The esophageal mucosa was found to be atrophic. There was no obstruction to the passage of the esophagoscope. Dilation was not carried out in this case. No further word has been received from this patient since his dismissal on Sept. 29, 1944.

SUMMARY

Approximately 10 per cent of patients suffering from acrosclerosis or scleroderma made complaints referable to the esophagus. The most common complaint was dysphagia. Frequently there was also substernal burning after meals, especially when the patient was lying down.

Positive roentgenographic or endoscopic evidence was demonstrated in 18 cases. Dilatation of the esophagus similar to that seen in cardiospasm was observed in 7 cases, and hiatal hernia with intrathoracic stomach was demonstrated in

9 cases. In 2 other cases, sclerodermic changes were demonstrated in the esophageal wall.

Acrosclerosis should be distinguished from other forms of scleroderma. In acrosclerosis the phenomena of Raynaud's disease are present prior to the dermatologic changes or coincident with them. Thirty-three of the 36 patients who had esophageal symptoms presented the clinical syndrome of acrosclerosis. All the 18 patients for whom conclusive roentgenographic or endoscopic evidence was obtained had acrosclerosis.

The basic alteration in acrosclerosis and scleroderma is sclerosis of the connective tissues of the body. Sclerodermic changes in the connective tissues of the esophagus are chiefly responsible for the esophageal disturbances. It should be emphasized that esophageal disturbances are extremely uncommon in Raynaud's disease per se. Reduction or absence of muscular activity in the wall of the esophagus and shortening of the esophagus apparently result from sclerodermic involvement. Disturbances of the autonomic nervous system may play some part in the causation. Clinical diagnoses of cardiospasm and hiatal hernia of the short esophagus type are made most frequently in these cases. Stenosis of the lower part of the esophagus and esophagogastric junction may occur with hiatal hernia as the result of chronic inflammation of the lower part of the esophagus. This inflammation is the result of incompetence of the cardiac sphincter with regurgitation of gastric secretions.

The treatment of the esophageal lesions of acrosclerosis consists of the passage of sounds over a previously swallowed thread. Fairly satisfactory results have been obtained. The esophageal stenosis of 1 of these patients has been treated satisfactorily over a sixteen year period by repeated dilations.

NEUROLOGIC COMPLICATIONS DURING MENINGOCOCCIC MENINGITIS TREATED WITH SULFONAMIDE DRUGS

LIEUTENANT (JG) THOMAS W. FARMER, MC-S, U.S.N.R.*

The purpose of this presentation is to outline the clinical course and prognosis in a variety of neurologic complications of meningococcic meningitis. During the epidemic years of 1942, 1943 and 1944, approximately 300 cases of meningococcic meningitis were reviewed by me at four hospitals.[1] About 100 cases involving children were included in this series. Of the 300 cases focal neurologic complications were observed to develop in 26 during the course of meningococcic infections. In each of these 26 cases it was ascertained that the paralysis did not exist before the onset of the meningeal infection and also that no other neurologic disease was present concomitantly with the meningitis. Detailed clinical information concerning the onset and severity of these sequelae was collected for this study.

An etiologic diagnosis was established in 24 of these 26 cases by the isolation of meningococci, group I, from the cerebrospinal fluid. In the remaining 2 cases presumptive diagnoses were based on the observations of meningeal signs, a petechial cutaneous eruption and purulent cerebrospinal fluid. All 26 patients received sulfonamide therapy: Sixteen received sulfadiazine; 7 were treated with sulfamerazine; 2 received sulfapyrazine, and 1 was treated with sulfathiazole. They all recovered.

The neurologic complications observed in these cases were of two groups: cranial nerve paralyses and cerebral disorders. Since cranial nerve palsies were much more common than cerebral complications, they are presented first.

CRANIAL NERVE PARALYSES

Descriptions of involvement of cranial nerves in meningococcic meningitis occur in the earliest reports of the disease. Before serum treatment was instituted, in 1907, paralyses of the sixth, seventh and eighth cranial nerves were repeatedly observed. Bilateral involvement of the auditory nerves with permanent deafness was well known as one of the serious complications in recovered patients. During the period of serotherapy, from 1907 to 1936, the same cranial nerve palsies were described. With chemotherapy reports of similar cranial nerve paralyses have appeared. These palsies usually involve a single nerve or pair of nerves. Involvement of multiple cranial nerves rarely occurs.

PARALYSIS OF THE SIXTH NERVE

Paralysis of the sixth cranial nerve with loss of function of the lateral rectus muscle prevents the eye from moving outward beyond the midline. Diplopia in the field of this paralysis is the result. Pseudoptosis of the eyelid on the side of the paralyzed muscle may be present. Abducens nerve palsy is the most common lesion of the extraocular muscles in meningococcic meningitis. It occurred frequently before the onset of serotherapy [2] and has remained common with serum and sulfonamide treatment.[3]

This article has been released for publication by the Division of Publications of the Bureau of Medicine and Surgery of the United States Navy. The opinions and views set forth are those of the writer and are not to be construed as reflecting the policies of the Navy Department.

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Dr. Derek Denny-Brown, Dr. Conrad Wesselhoeft and Dr. George Thorn, the chiefs of service at these hospitals, gave permission for the presentation of these cases.

1. These cases were studied at the Johns Hopkins Hospital in Baltimore and at the Boston City Hospital, the Massachusetts Memorial Hospitals (John C. Haynes Memorial) and the Peter Bent Brigham Hospital in Boston.

2. (*a*) Davis, A. E.: Eye Symptoms of Cerebrospinal Meningitis, M. News, New York **86:** 644, 1905. (*b*) Hutinel, V., and Voisin, R.: Maladies des méninges, in Gilbert, A., and Thoinot, L.: Nouveau traité de medecine et de thérapeutique, Paris, J. B. Baillière et fils, 1912, vol. 35.

3. (*a*) Sinclair, W.: The Ocular Complications of Cerebro-Spinal Fever, Tr. Ophth. Soc. U. Kingdom **39:** 233, 1919. (*b*) Neal, J. B.: Epidemic Meningitis, in Abt, I. A.: Pediatrics, Philadelphia, W. B. Saunders Company, 1925, vol. 6, chap. 158, p. 422. (*c*) McLean, S., and Caffey, J. P.: Endemic Meningococcus Meningitis: The Clinical Manifestations in Infancy and in Early Childhood, Am. J. Dis. Child. **35:** 357 (March) 1928. (*d*) Borovsky, M. P.: A Clinical

(Footnote continued on next page)

It occurs with similar frequency in children and in adults. The incidence of this complication has varied from 4 to 20 per cent in various epidemics, with an average of 10 per cent. Recently Harries [3f] reported strabismus in 15 per cent of 500 patients treated with sulfonamide drugs. Thus there has been no decline in the incidence of this complication as a result of sulfonamide treatment. Indeed, no decline should really be expected, since the sixth nerve is involved early in the course of the disease. In the majority of patients it is noted on the first physical examination after admission to the hospital.[3c] The involvement is most often unilateral. With recovery of the patient, the paralysis usually clears completely. Although the prognosis is good, rare cases of permanent abducens nerve paralysis have been noted.[3a, d] In such patients operative treatment, with advancement or resection of the external rectus muscle, may be advisable after diplopia has persisted for more than a year. However, the results are not uniformly successful.

In my study 9 patients with sixth nerve paralysis during meningococcic meningitis were carefully followed (table 1). The ages of the patients varied from 13 to 56 years. Paralysis developed early in the course of the meningeal infection. It appeared on the first to the fourth day in 8 patients and on the fifth day in 1. Weakness of the abducens nerve was noted in all 9 at the time of the patients' physical examinations when they were admitted to the hospital. Six of the patients presented relatively mild clinical pictures. All of these patients were conscious on entry to the hospital, and they complained of diplopia along with their meningeal symptoms. The other 3 patients were comatose. Seven of the patients had unilateral involvement, with partial or complete loss of function of one of the external rectus muscles. Two patients had complete bilateral sixth nerve paralysis. At the time of onset of paralysis the cerebrospinal fluid was purulent in every case, and usually it was under greatly increased pressure. All 7 patients with unilateral abducens nerve paralysis regained complete return of function of the nerve involved. In 5 of the 7 patients, function returned in less than two weeks. In the other 2 patients, recovery occurred in six and eleven weeks. Of the 2 patients with bilateral sixth nerve paralysis, 1 regained complete function of both external rectus muscles after eight months. The other regained complete function of the left abducens nerve one month after the onset of meningitis. However, paralysis of the right sixth nerve was still present at that time. Subsequent examination of this patient has been impossible.

TABLE 1.—*Sixth Nerve Paralysis During Meningococcic Meningitis*
Nine Patients, Boston and Baltimore, 1942-1944

Case (Hospital)	Age, Years	Onset of Sixth Nerve Paralysis: Day of Patient's Meningitis	Onset of Sixth Nerve Paralysis: Unilateral or Bilateral	Onset of Sixth Nerve Paralysis: Cerebrospinal Fluid	Complete Recovery of Sixth Nerve Function
Case 1 (BCH)	21	1st	Unilateral	Purulent	11 weeks
Case 2 (JHH)	17	1st	Unilateral	Purulent	5 days
Case 3 (PBBH)	34	2d	Unilateral	Purulent	1 week
Case 4 (JHH)	19	2d	Unilateral	Purulent	2 weeks
Case 5 (JHH)	26	3d	Unilateral	Purulent	1 day
Case 6 (JHH)	56	3d	Unilateral	Purulent	6 weeks
Case 7 (JHH)	13	4th	Unilateral	Purulent	6 days
Case 8 (JHH)	29	3d	Bilateral	Purulent	8 months (right) 8 months (left)
Case 9 (JHH)	36	5th	Bilateral	Purulent	1 month (left) Not known (right)

The clinical picture of unilateral and bilateral abducens nerve paralysis is illustrated by 2 case histories.

Unilateral Paralysis of the Sixth Nerve.

CASE 7.—D. S., a 13 year old Negro girl, was admitted to the Johns Hopkins Hospital on May 22, 1943, with stiff neck and chills of four days' duration. Four days before her admission severe headache and shaking chills developed. Milder headache persisted on the following day. Recurrent chills and stiffness of the neck developed on the day before her entry. On admission to the hospital she was complaining of severe headache, stiff neck and double vision.

Physical examination revealed a temperature of 103 F. (rectally). The patient was drowsy and had a stiff neck and bilateral Kernig signs. There was complete

Study of Meningococcus Meningitis and An Analysis of One Hundred and Ninety Cases Observed in a Period of Eighteen Months, Am. J. M. Sc. **179**: 82, 1930. (*e*) Lewis, P. M.: Ocular Complications of Meningococcic Meningitis: Observations in Three Hundred and Fifty Cases, Am. J. Ophth. **23**: 617, 1940. (*f*) Harries, G. E.: Cerebrospinal Fever: A Review of Five Hundred Cases Treated by Chemotherapy Without Intrathecal Serum, Brit. M. J. **2**: 423, 1942. (*g*) Keefer, C. S.: The Treatment of Bacterial Meningitis, M. Clin. North America **25**: 1287, 1941.

paralysis of the right external rectus muscle, with no other abnormal neurologic features.

Lumbar puncture at the time of her admission yielded purulent cerebrospinal fluid under an initial pressure of 410 mm. of fluid. The fluid contained meningococci, group 1. The patient received sulfamerazine therapy, and her temperature reached normal after three days. She continued to see double when she looked to the right. However, diplopia soon disappeared, and she regained full power of the right external rectus muscle six days after the onset of the nerve weakness. The meningeal signs disappeared at the same time, and she was discharged from the hospital in good health on June 4.

Bilateral Paralysis of the Sixth Nerve

CASE 8.—S. L., a 29 year old married white housewife, was admitted to the Johns Hopkins Hospital on March 12, 1942, with the complaints of headache and fever of three days' duration. A sore throat had developed three days before her admission. On the next day she had a shaking chill, followed by headache, vomiting and a cutaneous rash. On the day of entry she complained of double vision. Her temperature was 102 F. (rectally). She was cooperative and slightly drowsy and had stiffness of the neck and a positive Kernig sign. Examination of the cranial nerves revealed complete bilateral abducens nerve paralysis with pseudoptosis of the left eyelid (to prevent diplopia).

Lumbar puncture yielded purulent cerebrospinal fluid from which meningococci, group I, were grown on culture. She received sulfadiazine therapy, with prompt recovery from the meningeal infection. However, at the time of discharge from the hospital, on March 26, she was still complaining of double vision whenever she did not wear a patch over one eye. One month later examination revealed complete bilateral sixth nerve paralysis with diplopia. However, after several months she was able to move either eye outward to a slight degree. This ability increased, and her double vision soon disappeared. By November, eight months after her illness, she had regained complete function of both external rectus muscles.

PARALYSIS OF THE SEVENTH NERVE

Peripheral seventh nerve palsy results in loss of the function of all the muscles of facial expression on the affected side. This paralysis affects the forehead and eyelids as well as the musculature of the cheeks and mouth. With diplegia the face becomes masklike and motionless. The patient may also note a loss of the sense of taste on the anterior two thirds of the tongue as a result of interference of conduction through the chorda tympani.

Facial paralysis during the course of meningococcic meningitis has received only brief mention in the literature. An occasional reference to unilateral involvement of the seventh nerve appeared before the advent of serum therapy. Also a few patients with this complication treated with serum or sulfonamide drugs have been reported on.[4] The incidence of facial palsy has been recorded as 1 to 5 per cent. However, no adequate description of the clinical course of this complication and no references to facial diplegia have been found in the literature on the subject.

TABLE 2.—*Seventh Nerve Paralysis During Meningococcic Meningitis*
Nine Patients, Boston and Baltimore, 1942-1944

Case (Hospital)	Age, Years	Onset of Facial Nerve Paralysis: Day of Patient's Meningitis	Onset of Facial Nerve Paralysis: Unilateral or Bilateral	Onset of Facial Nerve Paralysis: Cerebrospinal Fluid	Recovery of Facial Paralysis
Case 10 (MMH)	15	5th	Unilateral	Not examined that day	5 months; complete
Case 11 (MMH)	6	5th	Unilateral	Not examined that day	2 days; complete
Case 12 (PBBH)	16	10th	Unilateral	Clear	1 year; complete
Case 13 (JHH)	31	11th	Unilateral	Not examined that day	3 weeks; complete
Case 14 (JHH)	30	12th	Unilateral	Not examined that day	1¼ years; incomplete
Case 15 (BCH)	22	9th	Bilateral	Clear	1 month; complete
Case 16 (MMH)	17	11th	Bilateral	Clear	3 months; complete
Case 17 (PBBH)	43	12th	Bilateral	Clear	1½ months; complete
Case 18 (JHH)	36	14th	Bilateral	Clear	1½ months; complete

Nine patients with peripheral seventh nerve paralysis after meningococcic meningitis were studied (table 2). The ages of the patients varied from 6 to 43 years. The course of the meningeal illness was relatively mild in 3 of the patients, while 6 had severe illnesses with delirium and coma. Weakness of the facial muscles developed from the fifth to the fourteenth day after onset of the meningeal signs and symp-

4. Hodes, H. L., and Strong, P. S.: Treatment of Meningococcic Meningitis with Sulfonamides, J. A. M. A. **119**:691 (June 27) 1942. Davis.[2a] Neal.[8b] Harries.[8f]

toms. In 5 patients the paralyses were unilateral, and in 4 facial diplegia developed. For 5 of the patients the cerebrospinal fluid was examined on the day of onset of this complication, and in each of these cases it was found that the fluid was clear and contained less than 100 leukocytes per cubic millimeter. For the other 4 patients the cerebrospinal fluid was not examined at the time of onset of the paralysis. Thus, in this group of patients involvement of the seventh nerve developed late in the meningeal phase of the illness, at a time when the cerebrospinal fluid had already cleared. Unilateral paralysis progressed to its maximum in one or two days. However, in the development of complete facial diplegia, from one to four days elapsed in the spread from one nerve to the other. In 2 of the 4 patients with bilateral seventh nerve palsy, loss of the sense of taste accompanied the paralysis.

Complete follow-up studies of all 9 patients were obtained. Recovery from facial paralysis was complete for 8 of the 9. Two of these patients regained function in less than one month, and for 6 complete recovery required from one to twelve months. The ninth patient (case 14), in whom paralysis of the right seventh nerve developed, regained the ability to raise her right eyebrow and to close her right eye tightly seven months after the onset of her illness. However, at that time her smile was still one sided. This lower facial palsy persisted, and it was still present one and one-quarter years after the onset of meningitis.

The report of 1 of the cases of unilateral seventh nerve paralysis is presented to illustrate the clinical picture of this complication. The 4 cases of facial diplegia are briefly outlined. All 4 of these cases are presented, because they follow such a characteristic clinical course, which apparently has not been described elsewhere.

Unilateral Paralysis of the Seventh Nerve.

CASE 12.—D. J., a 16 year old white schoolgirl, was admitted to the Peter Bent Brigham Hospital on June 11, 1942. She complained of abdominal pain, headache and vomiting of one day's duration. On the day before entry she had a shaking chill followed by headache, vomiting and pains in her wrist and knee joints. On admission she complained of abdominal pain and stiff neck. Three weeks before entry she had an acute suppurative otitis media on the right side, which cleared completely in one week.

Physical examination on her admission revealed a temperature of 100 F. (rectally). She was disoriented and confused. Stiff neck and Kernig's sign were present. No motor, sensory or reflex abnormalities were present and no abnormalities of the cranial nerves.

Lumbar puncture yielded purulent cerebrospinal fluid containing meningococci. Treatment with sulfadiazine was instituted, and the meningeal signs and symptoms disappeared in four days. On the tenth day after the onset of meningitis the patient noted that she was unable to smile on the right side of her face. She could not wrinkle the right side of her forehead. A pronounced right seventh nerve paralysis had developed with no other neurologic abnormalities. One month later the patient was able to wrinkle her forehead slightly on the right side. Complete return of function of the facial muscles required one year.

Bilateral Paralysis of the Seventh Nerve.

CASE 15.—C. M., a 22 year old white married housewife, was admitted to the Boston City Hospital on Sept. 19, 1942. She complained of severe headache, stiff neck and vomiting of two days' duration. She felt nauseated two days before entry. Nausea was followed by shaking chills. On the following morning a severe headache developed. Later in the day her neck became stiff, and she vomited. On the day of her admission to the hospital her headache and stiff neck grew worse. Her temperature was 101 F. (orally). She was slightly drowsy, with an extremely stiff neck and positive Kernig sign. No motor, sensory or reflex abnormalities were present and no abnormalities of the cranial nerves.

Lumbar puncture done at the time of her admission revealed purulent cerebrospinal fluid containing meningococci, group I. Sulfadiazine therapy was instituted, and her temperature fell to normal within two days. Her headache and stiff neck subsided by the fifth day, and she felt completely well. On the ninth day after the onset of meningitis she first noted a feeling of stiffness on both sides of her face and loss of the sense of taste. She was unable to raise her eyebrows, to close her eyelids, to smile or to show her teeth. Tears ran down over both cheeks. She was unable to distinguish salt and sugar placed on her tongue. In brief, a complete facial diplegia had suddenly developed. Examination of the other cranial nerves and of the sensory, motor and reflex systems showed no abnormalities. Lumbar puncture at this time revealed clear cerebrospinal fluid containing 11 leukocytes per cubic millimeter. One week after the onset of this bilateral seventh nerve paralysis, there was a flicker of movement in her eyelids and she was able to control the secretion of tears. She was discharged on the eighteenth day in the hospital with a residual bilateral facial weakness. She could close her eyelids against slight resistance, and she could move the right corner of her mouth. The sensation of taste was still absent. One month after the onset of the facial paralysis this patient returned for reexamination. She was able to smile normally, to raise her eyebrows and to close her eyes tightly. The sensation of taste had returned to normal. There was complete recovery of function of both seventh nerves.

CASE 16.—E. F., a 17 year old white youth, was admitted to the Haynes Memorial Hospital on June 17, 1943, with the complaints of headache and stiff neck of one day's duration. Four days before his entry fever and malaise, followed by a cutaneous eruption, developed. On the day before entry he complained of violent headache, vomiting and stiff neck. He was admitted in a comatose state. His temperature was 104 F. (rectally). He was alternately delirious and comatose. Stiff neck and positive Kernig sign were the only neurologic abnormalities.

Lumbar puncture done at the time of his admission revealed purulent cerebrospinal fluid containing menin-

gococci. Sulfamerazine therapy was instituted. After seven days his temperature returned to normal, and his meningeal signs subsided. On the eleventh day after the onset of meningitis a peripheral right facial paralysis developed, with normal movement of the left side of the face. At this time a lumbar puncture revealed clear cerebrospinal fluid containing 100 leukocytes per cubic millimeter. Four days later left facial paralysis developed. His face was masklike owing to facial diplegia. The sensation of taste was normal. Improvement was rapid, and one week later he had already regained approximately 75 per cent of the function of the left side of his face and 50 per cent of the right. Recovery was complete in three months.

CASE 17.—F. S., a 43 year old white man, a lathe operator, was admitted to the Peter Bent Brigham Hospital on April 12, 1943, complaining of stiff neck and headache of two days' duration. Two days before his admission he had a shaking chill followed by headache, vomiting and a cutaneous rash. The headache and stiff neck persisted until his entry. His temperature was 101 F. (orally). He had a stiff neck, positive Kernig sign and moderate papilledema.

Lumbar puncture done at the time of his admission revealed purulent cerebrospinal fluid containing meningococci, and sulfadiazine therapy was begun. Meningeal signs disappeared after five days. On the twelfth day after the onset of meningitis a complete bilateral facial paralysis suddenly developed. The sensation of taste was normal. Lumbar puncture revealed clear cerebrospinal fluid containing 4 cells per cubic millimeter. Two weeks later there was noticeable improvement. He was able to close his eyes and to smile. However, he could not wrinkle his forehead. Function returned more rapidly on the right side. After one and one-half months recovery was complete.

CASE 18.—E. N., a 36 year old white man, was admitted to the Johns Hopkins Hospital on Sept. 22, 1942, with the complaints of headache and vomiting of two days' duration. A sore throat developed two days before his entry. On the next day he had a headache, and he vomited. He became lethargic and later semicomatose on the day of his admission. His temperature was 102 F. He had an extremely stiff neck and bilateral Kernig sign. There were no other neurologic abnormalities.

Lumbar puncture done at the time of his entry revealed purulent cerebrospinal fluid containing meningococci. He was treated with sulfadiazine, and his meningeal infection subsided during the next five days. On the fourteenth day after the onset of meningitis a complete left facial paralysis developed. At this time lumbar puncture revealed clear cerebrospinal fluid containing 100 leukocytes per cubic millimeter. Two days later an additional right facial paralysis developed. With this facial diplegia he noted loss of the sensation of taste. He was unable to distinguish salt from sugar on either side of his tongue. Two weeks after the onset of facial palsy he could close both eyelids against slight resistance. He could wrinkle the left side of the forehead and smile on the right side of his mouth. Soon the sensation of taste returned. After one and one-half months the facial diplegia had completely cleared.

PARALYSIS OF THE EIGHTH NERVE

Destruction of the eighth cranial nerves with their cochlear and vestibular divisions results in deafness and unsteadiness in walking. In small children permanent bilateral deafness results in deaf-mutism.

Permanent deafness is one of the serious complications of meningococcic meningitis. This deafness is a direct result of the meningitis, and it is not related to otitis media, which often accompanies this disease in children. Before the use of serum treatment the incidence of involvement of the eighth nerve among recovered patients ranged from 5 to 30 per cent in different epidemics. With serum therapy deafness followed meningitis in 2 to 25 per cent of cases, with an average of approximately 5 per cent.[5] Since sulfonamide therapy has been instituted, no noticeable decline in the average incidence of acoustic nerve palsy has occurred. The present frequency ranges from 2 to 6 per cent, with an average of 5 per cent.[6] Permanent bilateral deafness is more common among children than among adults. The onset usually occurs during the first week of meningitis.[2b] However, it may develop after recovery, when the cerebrospinal fluid is clear.[7] In 2 reported cases bilateral deafness developed two and one-half and three months after complete recovery from meningitis with serum treatment.[3d]

In the majority of cases eighth nerve paralysis is bilateral, although unilateral involvement does occur. In about two thirds of those patients with total deafness, there are concomitant disturbances of the vestibular apparatus.[8] Auditory nerve palsy is usually permanent, although there are occasional cases in which the patients have completely recovered hearing.[6b] Vestibular symptoms disappear rapidly in adults, but in children they may persist for a year or longer. In children under 8 years of age complete deafness usually results in deaf-mutism.[2b] Thus meningococcic meningitis is one of the common causes of deaf-mutism.[9] In older children and

5. Fraser, J. S., and Dickie, J. K. M.: Meningitic Neuro-Labyrinthitis, Proc. Roy. Soc. Med. (Sect. Otol.) **13**: 23, 1920. Borovsky.[3d]

6. (*a*) Memorandum on Cerebro-Spinal Fever Among Troops, Great Britain War Office, London, His Majesty's Stationery Office, June 30, 1942. (*b*) Beeson, P. B., and Westerman, E.: Cerebrospinal Fever: Analysis of 3,575 Case Reports, with Special Reference to Sulphonamide Therapy, Brit. M. J. **1**: 497, 1943. (*c*) Harries.[3f] Hodes and Strong.[4]

7. McLean, S., and Caffey, J. P.: Sporadic Meningococcus Meningitis: Sequelae Following Specific Serum Therapy in Infancy and Early Childhood, J. A. M. A. **87**: 91 (July 10) 1926. Neal.[3b]

8. Politzer, A.: Diseases of the Ear, ed. 6, edited by M. J. Ballin, Philadelphia, Lea & Febiger, 1926.

9. Shambaugh, G. E.; Hayden, D. B.; Hagens, E. W., and Watkins, R. W.: Statistical Studies of the Children in Public Schools for the Deaf, Arch. Otolaryng. **12**: 190 (Aug.) 1930.

in adults with complete deafness, speech disorders develop, and special training is required for these patients.

Pathologic studies have shown that permanent deafness after meningitis is usually due to a neurolabyrinthitis.[10] The infection passes along the subarachnoid space from the base of the brain to the internal auditory meatus and then along the nerves and vessels to the labyrinths. A variety of pathologic changes producing deafness have been studied. These include: (*a*) hydrocephalus, (*b*) changes in the walls of the fourth ventricle, (*c*) purulent infiltration of the eighth nerve and (*d*) purulent labyrinthitis. The pathologic changes producing transient deafness with complete recovery have not been described.

Five patients with deafness after meningitis were studied (table 3). Four of these were

TABLE 3.—*Eighth Nerve Paralysis During Meningococcic Meningitis*
Five Patients, Boston and Baltimore, 1942-1944

Patient (Hospital)	Age, Yr.	Deafness, Unilateral or Bilateral	Severity of Deafness	Permanence of Deafness: Duration of Follow-Up	Permanence of Deafness: Recovery of Hearing
Case 19 (JHH)	33	Unilateral	Complete	1¼ years	None
Case 20 (JHH)	6	Bilateral	Nearly complete	2 years	Minimal
Case 21 (BCH)	5	Bilateral	Complete	2 years	None
Case 22 (JHH)	1	Bilateral	Complete	2½ years	None
Case 23 (JHH)	7	Bilateral	Nearly complete	1¼ years	Minimal

children from 1 to 7 years of age, and in all 4 of them bilateral involvement developed. Unilateral eighth nerve paralysis developed in a 33 year old woman. In 2 patients deafness was first observed on the third and on the seventh day after the onset of meningitis. In the other 3 the time of onset could not be accurately determined. In all patients deafness was complete or nearly complete. In 3 of the children unsteadiness in walking was noted after recovery. These 5 patients were all followed for periods of one and one-quarter to two and one-half years. In 3 patients there was no recovery of hearing at all, and in the other 2 recovery was minimal. An unsteady gait persisted for two years in 2 of the children, whereas 1 child walked normally one month after recovery. In addition, the children with bilateral deafness acquired speech disorders. One infant, who had meningitis at the age of 1 year, was a deaf-mute at 3½ years of age. The other 3 children talked, but they spoke too fast to be understood. On returning to school they were no longer able to do satisfactory work. Therefore they are now attending special schools for the deaf. The late treatment of these otherwise normal children includes training in lip reading and voice in order that they may continue their intellectual development.

The clinical pictures of unilateral and bilateral eighth nerve paralysis are illustrated by the following 2 case histories.

Unilateral Paralysis of the Eighth Nerve.

CASE 19.—M. P., a 33 year old white married woman, was admitted to the Johns Hopkins Hospital on March 31, 1943, with the complaints of headache, vomiting and stiff neck of three days' duration. A headache had developed three days before her admission. This became more severe on the following day. A stiff neck and vomiting developed on the day of her admission. Her temperature was 99.8 F. She was delirious and had pronounced meningeal signs. No focal neurologic signs were elicited.

Lumbar puncture done at the time of her admission revealed purulent cerebrospinal fluid containing meningococci. She was treated with sulfamerazine. After her meningeal infection subsided, she complained of ringing in the right side of her head. Examination of the ears ten days after the onset of meningitis revealed complete loss of bone and air conduction in the right ear. However, the exact day of the onset of deafness was not known. For the next few months the deafness in the right ear remained unchanged. She was troubled with tinnitus and repeated "explosions in the head." These symptoms gradually subsided during the first year. On reexamination one and one quarter years after the onset of meningitis she was still found to have complete deafness in her right ear with no other complaints.

Bilateral Paralysis of the Eighth Nerve.

CASE 20.—R. T., a 6 year old white boy, was admitted to the Harriet Lane Home at the Johns Hopkins Hospital on Oct. 3, 1942, with headache, stiff neck and convulsions of one day's duration. On the day before his entry he complained of a headache and stiff neck. He had a generalized convulsion. On the day of admission he became drowsy and confused. His temperature was 103 F. He was disoriented, and he had definite meningeal signs. Lumbar puncture done at the time of his entry revealed purulent cerebrospinal fluid containing meningococci. Treatment with sulfapyrazine was instituted. By the third day after the onset of meningitis he was much improved, and he recognized his visitors. However, he said that he was unable to hear them. Thus, during the early stage of this meningeal infection complete deafness had developed in his right ear and severe deafness in his left ear. One month later his hearing had improved slightly in the left ear, so that he was able to hear words shouted at him. However, he remained totally deaf in the right ear. His gait was slightly unsteady. On reexamination five months after the onset of deafness his hearing was found to be unimproved. Two

10. Hagens, E. W.: Pathology of the Inner Ear in a Case of Deafness from Epidemic Cerebrospinal Meningitis, Ann. Otol., Rhin. & Laryng. **49**: 168, 1940. Fraser and Dickie.[5] Politzer.[8]

years after his illness he was still completely deaf in the right ear and severely deaf in the left ear. Slight swaying in walking was still present.

PARALYSIS OF OTHER CRANIAL NERVES

Involvement of the second cranial nerves with changes in the optic disks is common in meningococcic meningitis. Lewis [3e] noted "papillitis" in 12 per cent of 350 cases. These changes are nearly always bilateral and subside with recovery of the patient. Rarely, partial secondary atrophy of the optic nerve or blindness follows.

Partial third nerve paralysis with transient divergent strabismus [11] or ptosis [12] have occasionally been noted. In 1 patient I observed, complete left third nerve paralysis developed, with ptosis, dilated pupil and divergent strabismus, during the course of meningococcic meningitis. However, this patient also had untreated syphilis of the central nervous system, so that the etiologic basis of the cranial nerve complication was uncertain.

Rare cases of fifth nerve paralysis [2a] and of pharyngeal paralysis [3f] during meningococcic meningitis have been described.

CEREBRAL COMPLICATIONS

In patients with severe meningeal infections, abnormal mental states develop, including disorientation, confabulation, hallucinations, convulsions, tremors and coma.[13] In particular, persons chronically addicted to alcohol who have meningitis frequently present confusional psychoses, and they may be admitted to mental hospitals with the mistaken diagnosis of delirium tremens.[14] Approximately one third of children with meningitis have generalized convulsions.[3b, e] Such cerebral symptoms as these are part of the meningitic picture and are not regarded as cerebral complications of meningitis.

Hemiplegia and aphasia, however, represent definite cerebral involvement. These unusual complications were first reviewed in the French literature.[2b] In 1898 Florand [15] described the case of a 13 year old child in whom aphasia and right-sided hemiplegia developed on the twelfth day of meningitis. The cerebrospinal fluid was clear at that time, but the patient died on the following day. In another report [16] left-sided hemiplegia was said to have developed in a 17 year old patient twenty-three days after the onset of meningitis. At this time the cerebrospinal fluid was clear. Reexamination of the patient two months later revealed persistent spastic hemiplegia. Recently Harries [3f] noted 1 patient with transient hemiplegia among 500 patients with meningitis treated with sulfonamide drugs. Thus, focal cerebral complications in meningococcic meningitis do occasionally occur despite sulfonamide therapy. The pathologic process which produces this clinical picture is not known. However, it must be distinguished from brain abscess.

TABLE 4.—*Cerebral Complications During Meningococcic Meningitis*

Three Patients, Boston City Hospital, 1942-1943

		Onset of Complication			
Patient	Age, Yr.	Day of Patient's Meningitis	Cerebrospinal Fluid	Clinical Picture	Complete Recovery from Complication
Case 24	9	7th	Clear	Right-sided convulsions	1½ hours
				Right hemiparesis	1 day
				Right homonymous hemianopia	1 month
				Aphasia	2 months
Case 25	9	6th	Not examined that day	Right-sided convulsions	4 hours
				Right hemiparesis	10 days
				Aphasia	4 months
Case 26	65	9th	Clear	Generalized convulsions	4 days
				Left hemiparesis	3 weeks

In my study 3 patients with meningococcic meningitis complicated by hemiplegia were observed (table 4). Two of these were children, each of whom was 9 years old. The third patient was a 65 year old man. These 3 patients were treated early in the courses of their infections, and they did not present unusually severe clinical pictures. One patient had only meningeal signs and symptoms on his admission to the hospital; 1 was irrational, and the third was comatose. The complication had its onset from the sixth to the

11. Randolph, R. L.: A Clinical Study of Forty Cases of Cerebro-Spinal Meningitis, with Reference to the Eye Symptoms, Bull. Johns Hopkins Hosp. **4:** 59, 1893.

12. Neal.[3b] Borovsky.[3d] Harries.[3f]

13. Hoesch, K.: Ueber epidemische Meningitis mit Encephalitis und über Meningo-Encephalitis (Encephalitis japonica), Zentralbl. f. inn. Med. **61:** 161, 1940.

14. Weir, T. W. H., and Vautier, C. K.: Mental Symptoms in Cerebrospinal Meningitis, Brit. M. J. **1:** 179, 1942.

15. Florand, A.: Un cas de méningite cérébro-spinale épidémique, Bull. et mém. Soc. méd. d. hôp. de Paris **15:** 530, 1898.

16. Castaigne, J., and Rivet, L.: Méningite cérébro-spinale épidemique compliquée d'hemiplégie: Comparaison chez un même malade des effets thérapeutiques de l'électrargol et du sérum de dopter, Bull. et mém. Soc. méd. d. hôp. de Paris **27:** 900, 1909.

ninth day after the onset of definite meningeal signs and symptoms. At this time the cerebrospinal fluid was already clear. The onset of this complication was heralded by a series of convulsions lasting from a few hours to a few days. In 2 patients seizures were unilateral, and in the third they were generalized. Convulsions left the patient with a hemiparesis of one to twenty-one days' duration. In 1 patient there was a complete homonymous hemianopsia, which gradually cleared during one month. In 2 patients an aphasic disorder developed, which disappeared in two to four months. In 1 patient right homonymous hemianopsia, hemiparesis and aphasia were associated with a definite slow wave focus in the left parieto-occipital area as observed by electroencephalogram. As the clinical symptoms disappeared, the electroencephalogram showed a less definite focus. This patient's aphasic disorder completely disappeared in two months. The electroencephalogram became normal after six months. In none of these patients have any sequelae developed from this cerebral complication. Neither of the children has had any convulsions during the first year after recovery.

The clinical course of 2 of these patients is presented here.

CASE 24.—J. F., a 9 year old white schoolboy in the third grade, was admitted to the Boston City Hospital on May 8, 1943, with the complaints of headache and vomiting of one day's duration. On the day before entry this boy came home from school because of headache, vomiting and fever. On the morning of admission he again vomited several times, and his neck and back became stiff. In a few hours he became comatose, and he was admitted to the hospital. Prior to his illness he had had no convulsions.

Physical examination on admission revealed an acutely ill boy with a temperature of 103 F. (rectally). He was comatose. His jaws were closed tightly. His neck was extended and quite stiff. His legs were flexed at the knees, and they could not be completely extended. No motor, sensory or reflex abnormalities were noted and no abnormalities of the cranial nerves.

Lumbar puncture done at the time of his admission revealed purulent cerebrospinal fluid from which meningococci were grown on culture. Sulfadiazine therapy was instituted. On the following day he recognized his mother, but headache, stiff neck and fever persisted. By the fifth day, his temperature had fallen to 99 F.; the meningeal signs had diminished, and he looked much brighter. However, on the seventh day after the onset of meningitis he had a right-sided convulsive seizure with loss of consciousness. His head and eyes turned to the right with clonic movements of the right arm and leg for forty-five seconds. During this seizure he was incontinent of urine. This was followed by brief episodes of twitching of the right arm, which recurred at five minute intervals for the next ninety minutes. He was given phenobarbital subcutaneously, and the twitching soon ceased. It was observed that his right arm was weak. Lumbar puncture at this time revealed clear cerebrospinal fluid. On the following day he was drowsy but cooperative. A mild aphasic disturbance was noted. For example, he was unable to name certain common objects (watch and buckle). He was unable to write many simple words. In attempting to write the alphabet he wrote "a, b, c" but no further. He could write his name, his address and certain numerals correctly. He could read words well, and he could carry out simple commands. In addition, it was noted that he had a definite right homonymous hemianopsia. There was no facial weakness and no weakness of the right arm or leg. An electroencephalogram at this time revealed a definite, large slow wave focus (3 per second) in the left parieto-occipital area. Two days later the boy was able to sit up, and he felt rather well. His aphasic disorder had improved. He was now able to write the alphabet, but he still misspelled simple words. The right homonymous hemianopsia remained nearly complete. However, within one month after the onset of this hemianoptic disorder his visual fields returned to normal. At this time, he still had some difficulty in writing words which had been familiar to him before his illness. During the next month he had to relearn the miltiplication tables, his prayers, the use of capital letters and other parts of his previously collected knowledge. Two months after his illness he was again able to read and write normally. The electroencephalogram at this time revealed less pronounced abnormalities than previously. However, there were still bursts of slow waves, chiefly in the left occipital area. Subsequent electroencephalograms revealed a gradual return to the normal pattern in six months after his illness. He did satisfactory school work during the following year, and he had no episodes of unconsciousness or convulsions in this period.

CASE 25.—W. S., a 9 year old white schoolboy in the third grade, was admitted to the Boston City Hospital on March 17, 1943, with fever, headache and vomiting of two days' duration. A sore throat developed two days before his entry. The following day he complained of headache, backache and vomiting. On the day of entry he became irrational, with severe headache and vomiting. He thought that some one was stealing his sister from their home.

When this boy was 2 years of age, he had an infection of the left middle ear with mastoiditis. At this time a mastoidectomy on the left side was performed. During this illness no convulsive disorders were observed. However, during the following year he had four grand mal seizures, each one of ten to fifteen minutes' duration. These seizures ceased to occur after he was 3 years old, so that he had had no convulsions during the past six years.

Physical examination on his admission to the hospital revealed a temperature of 102 F. (rectally). The left ear drum was perforated, and there was an old mastoidectomy scar. He was disoriented and irrational, with stiff neck and Kernig's sign. Examinations of the cranial nerves and of the motor, sensory and reflex systems revealed nothing abnormal.

Lumbar puncture done at the time of his admission revealed purulent cerebrospinal fluid containing meningococci. Sulfadiazine therapy was instituted. During the first three days he improved slowly. He became oriented, and his fever subsided. However, on the sixth day after the onset of meningitis he had a series of four convulsions, which involved the right side of his body. These seizures occurred over a four hour period, and they were followed by aphasia and right hemiparesis. On the following day, his temperature

was 99 F., and his hemiparesis and aphasic disorder had improved. A slight weakness of the lower right side of the face was noted. During the next ten days the right-sided weakness gradually disappeared. However, the aphasic disorder persisted. He named most common objects incorrectly. He was unable to write his name. He could write only the first seven letters of the alphabet. He was unable to read simple words. However, he was able to demonstrate the use of objects presented to him. One month after the onset of this aphasia he was still unable to name objects. However, he was able to write his name and the alphabet. He read letters but not words. During the next three months he learned to read and write again. Thus, four months after his illness he could read letters and words fairly well. He could write simple words correctly, and he could add, subtract and multiply. When he returned to school, his work was satisfactory. Subsequently he has had no convulsive seizures.

in the course of meningitis, when the cerebrospinal fluid is purulent. It is usually unilateral, and complete recovery within a few weeks is the rule.

2. Unilateral and bilateral seventh nerve paralyses are usually late complications, which develop after the cerebrospinal fluid has become clear. In 4 patients with facial diplegia this late onset of paralysis during convalescence was characteristic. Recovery of function usually requires several months. It is complete in most but not all of the cases.

3. Eighth nerve paralysis with deafness is the most serious cranial nerve complication. It occurs more commonly among children than among adults, and it usually is bilateral. Its present incidence is approximately 5 per cent. It may develop during the acute meningitic infection, convalescence or even after recovery. Deafness is permanent in the vast majority of cases. In young children deaf-mutism results. Occasional cases of transitory deafness also occur.

Cerebral complications with convulsions and transient hemiplegia occur rarely. They usually appear late in the course of the infection with clear cerebrospinal fluid. The convulsions may be unilateral or generalized. They are followed by hemiparesis with occasional aphasic disorders and hemianopsia. Electroencephalograms reveal focal disturbances in the area involved. All of these neurologic and electroencephalographic signs were observed to clear completely, with no residua.

TABLE 5.—*Outline of the Clinical Features of Cranial Nerve Paralyses During Meningococcic Meningitis*

Cranial Nerve Involved	Age	Incidence Reported at Present, per Cent	Unilateral or Bilateral	Onset of Complication		Usual Prognosis
				Stage of Meningitis	Cerebrospinal Fluid	
Sixth	All ages	5 to 15	Both, usually unilateral	Acute	Purulent	Complete; recovery in 1 to 4 weeks
Seventh	All ages	1 to 5	Both, usually unilateral	Convalescent	Clear	Complete; recovery in 1 to 12 months
Eighth	Usually children	2 to 6	Both, usually bilateral	Acute or convalescent	Purulent or clear	Permanent; deafness

SUMMARY

From the large group of possible sequelae occurring in patients with meningococcic meningitis, certain neurologic complications were selected for study. Twenty-six patients with focal neurologic abnormalities among a group of 300 patients with meningococcic meningitis were carefully followed during the past three years. This series included 9 patients with sixth nerve paralysis, 9 with seventh nerve paralysis, 5 with eighth nerve paralysis and 3 with transient focal cerebral complications.

Cranial nerve paralyses present characteristic clinical features. (The usual course of each one is outlined in table 5.)

1. Sixth nerve paralysis, the most common extraocular nerve palsy, usually develops early

AN ACCOUNT OF STOCK

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Each state chairman of the Procurement and Assignment Service for Physicians is faced with the baffling task of keeping track of the migratory habits of his colleagues. Among other bits of information this entails on his part a knowledge of those of the medical profession who die at any time in any city or town within his area and of those by whom they are replaced. Hence it has happened that during my term of service as state chairman for Massachusetts I have perforce explored with increasing diligence a curious source for medical research—the obituary columns of *The Journal of the American Medical Association.*

In a representative issue more than seventy deaths may be reported. If one happens to be morbidly inclined, one suspects that vascular disease affecting either the heart, the kidneys or the cerebral vessels is a disorder to which the medical profession has special predisposition. In 1944, in the December 1 issue of *The Journal,* to take an offhand sample, seventy-one deaths were reported. There were thirteen deaths from coronary artery disease, sixteen from unspecified heart disease on an arteriosclerotic background, five from generalized arteriosclerosis in which the exact cause of death was not noted, four from cerebral hemorrhage or thrombosis, two from nephritis and one from myocarditis.

Records such as this, issue after issue, have interested many observers. Each year *The Journal* is likely to comment in an editorial on the annual cost of cardiovascular disease to our profession, and several clinicians have written about it. White,[1] for example, found among one hundred physicians examined for cardiac symptoms that seventy-six had organic disease of the heart or blood vessels. Willius [2] has called today's death rate from heart disease among physicians appalling. Falk [3] has expressed the view that coronary disease is taking a disproportionate toll each year from the ranks of the medical profession, and Musser [4] appeared to agree with him. Smith,[5] approaching the problem from a slightly different angle, has shown that the incidence of coronary sclerosis among physicians who have consulted the Mayo Clinic was considerably higher than that among bankers, lawyers, clergymen or laborers, and Kellogg,[6] studying physicians and other candidates of comparable age who applied for Army commissions, also found that the incidence of heart disease, hypertension and renal disease was appreciably greater among physicians than among others.

Such observations are impressive. On the other hand, there is another side to the story. Ten years ago Riesman and Harris [7] pointed out that the increase in number of deaths reported from heart disease year by year is not a fortuitous happening but in reality represents a triumph of preventive medicine. For by the prolongation of the average span of life, more persons are kept alive to die from those diseases that naturally afflict advancing years. And Chadwick,[8] evidently thinking along similar lines, has predicted that the mortality from diseases of the heart and blood vessels is bound to increase so long as the average age of the population continues to lengthen.

It is possible, therefore, that the increasing incidence of vascular disease among physicians may be more apparent than real, is in many instances the price of longevity and is in no way remarkable. Since there are differing views on a matter of such general professional interest and since the rational conservation of medical manpower is at present so desirable, it seemed worth

1. White, P. D.: The Physician Himself, J. A. M. A. **115**:1495-1499 (Oct. 26) 1940.

2. Willius, F. A.: A Talk on Cardiac Disease Among Physicians, Proc. Staff Meet., Mayo Clin. **16**: 714-716 (Nov. 5) 1941.

3. Falk, O. P. J.: Coronary Disease and the Doctor, Illinois M. J. **80**:115-119 (Aug.) 1941.

4. Musser, J. H.: The Doctor's Heart, Ohio State M. J. **40**:123-125 (Feb.) 1944.

5. Smith, H. L.: Incidence of Coronary Sclerosis Among Physicians, J. A. M. A. **108**:1327-1329 (April 17) 1937.

6. Kellogg, F.: Physical Defects Among Physicians and Other Applicants for Commission, Army M. Bull., July 1943, no. 68, pp. 158-165.

7. Riesman, D., and Harris, S. E.: Disease of the Coronary Arteries with a Consideration of Data on the Increasing Mortality of Heart Disease, Am. J. M. Sc. **187**:1-15 (Jan.) 1934.

8. Chadwick, H. D.: The Diseases of the Inhabitants of the Commonwealth, New England J. Med. **216**: 1003-1015 (June 10) 1937.

while to attempt an account of stock. The conclusions must be regarded as being of a preliminary nature. For at the 1944 meeting of the House of Delegates of the American Medical Association the Board of Trustees[9] made the following statement:

The deaths of physicians have continued at almost the same rate annually for many years. The number varies from a high of slightly more than 3,700 in 1939 to nearly 2,900 in 1931.

Last year a study was begun to determine the facts concerning the causes and rates of death among physicians in order that there may be shown a better comparison of the death rates in the general population with those in the medical profession. The Association will benefit in this study by the skill and experience of a well known statistician, Dr. Louis I. Dublin.

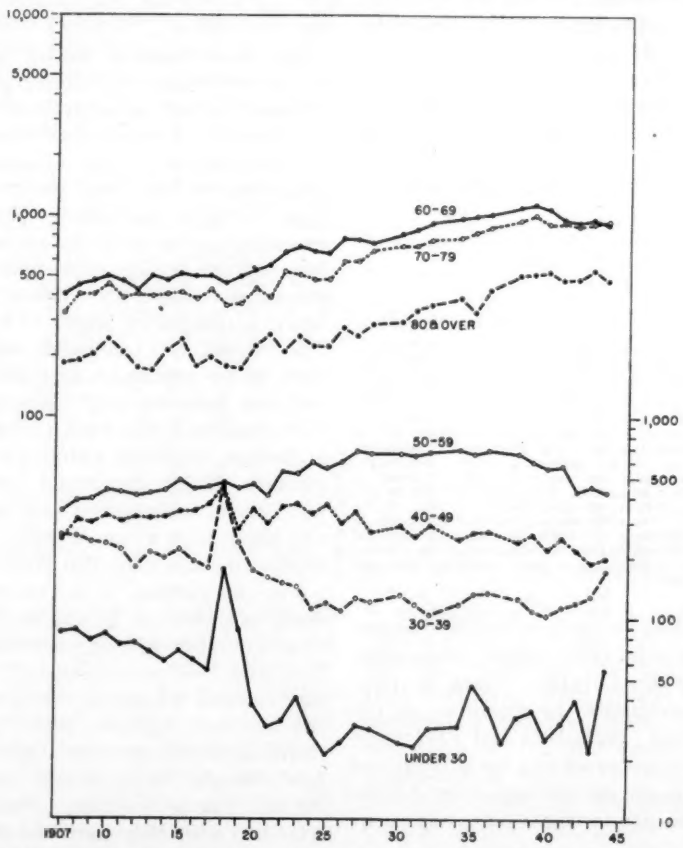
Since this seems to be the first study of the kind for the determination of mortality rates for a professional group, much interest should develop in the results of the work, and since all the figures from this work will represent an original contribution as to both methods and rates, there should be considerable satisfaction in developing a process that should be of value to professional groups.

It is impossible to state at present the exact time when these data will be available. However, as soon as the work is completed an announcement of the details of publication and distribution of the data will be made.

9. Report of Board of Trustees, J. A. M. A. **124:** 1262-1294 (April 29) 1944.

THE ANNUAL NUMBER OF DEATHS OF PHYSICIANS

At the outset a graph was plotted of the number of deaths of physicians reported year by year by *The Journal of the American Medical Association* since 1907. These data were broken down into age groups by decades, commencing with deaths occurring among physicians who were under 30 years of age. The year 1907 was selected as the starting point, because the first edition of the "American Medical Directory" was then published and an accurate tabulation of the size of the medical population was henceforward possible.



Deaths each year since 1907 among physicians by age groups (as reported by *The Journal of the American Medical Association*).

An unmistakable trend has developed which now has been maintained for more than thirty

years. Year by year, fewer physicians under 60 years of age are dying, and more are living to attain 70 and 80 year marks. It is of passing interest that the only demonstrable effect of the First World War on the curves was caused by the influenza epidemic. The present war is unlikely to have any notable effect on the medical profession unless another pandemic of high virulence afflicts the world.

The graph also suggests, by indirection, an aging medical population. No record could be found of the age distribution of physicians in the United States at different periods, and therefore such a record was manufactured. To tabulate by age groupings all the physicians listed in each edition of the "American Medical Directory" would have defied the energy of a behemoth. To regard a single state as representative and to apply figures for that state from time to time to the medical population of the entire country

TABLE 1.—*An Estimation of the Age Distribution of American Physicians* *

Year	Physicians, Total	Under 40	40 to 49	50 to 59	60 and Over
1907	122,200	59,880 (49%)	30,550 (25%)	18,330 (15%)	13,440 (11%)
1921	145,400	50,890 (35%)	43,620 (30%)	27,630 (19%)	23,260 (16%)
1931	156,400	56,300 (36%)	35,970 (23%)	34,410 (22%)	29,720 (19%)
1942	180,500	77,600 (43%)	37,910 (21%)	27,080 (15%)	37,910 (21%)

* In 1942, the Committee on Medical Preparedness of the American Medical Association estimated that at the beginning of the year there were 176,191 physicians in the continental United States. Twenty-four per cent were under 36 years of age, 22 per cent between 36 and 44, 18 per cent between 45 and 54 and 36 per cent 55 years of age and older (J. A. M. A. **119**: 650-653 [June 20] 1942). These figures suggest that the mode of reckoning used in assembling this table may have exaggerated the number of young physicians and underestimated the number who are older. These miscalculations would make no difference in the conclusions drawn.

seemed a reasonable way of meeting the situation and of acquiring sufficiently reliable information for the purposes of this paper. Thus, the physicians of Massachusetts, as appearing in the directories for 1907, 1921, 1931 and 1942, were counted and were separated into age groups, and from these figures the age makeup of the American medical profession for these years was calculated.

The figures support the premise that the average age of physicians at the time of death has been rising, together with an increasing percentage of all physicians living in the later decades of life. It was between 1907 and 1921 that many of the weaker schools closed, and enrollments were low; and it was in 1918 to 1920 that many young physicians succumbed to influenza. The influence of these factors is brought out by the relatively small number of physicians in 1921 who were less than 40 years old. Ten years later, in 1931, and twenty years later, in 1942, as men of the relatively small classes and the survivors of the influenza epidemic grew older, their low numbers were reflected in the makeup of the medical population as a whole. Yet, in spite of this handicap, the total number of physicians living to pass the age of 60 has increased steadily.

Since 1921, schools have enlarged and new schools have come into existence. Presumably, therefore, in future, physicians of all age groups are likely to increase. With the number of elderly men growing so steadily, the question must soon arise how best to utilize their talents and indeed how best to support them when they retire.

THE CAUSES OF DEATH AMONG PHYSICIANS

The most common causes of death among physicians by ages at different periods were determined through an analysis of death notices in *The Journal*. Various other observers have used this information. Three especially entertaining investigations have been reported, resulting in three divergent conclusions—perhaps a salutary reminder to a novice in the statistical field of the difficulty of dealing with figures. Rendich [10] attempted to discover whether medical prominence, as judged by length of a death notice in *The Journal*, was compatible with longevity and came to the conclusion that men who achieved sufficient fame for long obituaries were shorter lived than their less known colleagues. Mills,[11] in contrast, disagreed with this and, using similar methods, thought he proved that the great were not inclined to die young and that their heritage was likely to be a ripe old age. And Lehman [12] expressed the opinion that both were wrong!

For the purpose of this study the causes of death in a series of groups of 250 or more physicians of different ages occurring at about 1907, 1931 and 1942 were tabulated. The year 1921 was omitted, because in that year the effects of the influenza epidemic were still evident and therefore death rates were atypical. Deaths from battle injuries in the present war were also excluded. The age groupings comprised physicians who died when they were less than 40 years old, 40 to 49, 50 to 59 and 60 years old and over. It seemed desirable to assemble at least 250 cases in each of these age groups in order to have a reasonably large number from which to obtain a picture of the distribution of the common types of fatal illness at about the time under consideration, and in order to collect material of such size

10. Rendich, R. A.: Average Age of Physicians at Death, Correspondence, J. A. M. A. **119**:1041 (July 25) 1942.

11. Mills, C. A.: What Price Glory? Science **96**: 380-381 (Oct. 23) 1942.

12. Lehman, H. C.: The Longevity of the Eminent, Science **98**:270-273 (Sept. 24) 1943.

it was necessary to cull more than one year's yield. In scanning the reports from the early days, it was hard to find the cause of many fatalities among older men in any single year, whereas now it is difficult to find many fatalities among younger ones. Diagnoses were made as accurately as possible from the information presented—admittedly a matter of personal judgment since fashions in medical terminology have been fickle. In 1907 "acute indigestion" was often reported as a fatal illness, but no hesitancy is felt, through light of current knowledge, in including such cases among cardiac deaths. After the publication of Herrick's [13] paper, the diagnosis of coronary thrombosis began to appear and has flourished ever since. Epstein's [14] study of albumin and globulin ratios in edema commenced to make the diagnosis of nephritis less common, and Christian's [15] teaching of the importance of differentiating between cardiac and renal dropsy also played a part in increasing the number of reports of cardiac deaths at the expense of those previously reported as due to renal disease. Accidental deaths and deaths by suicide were grouped together as accidents, because in many instances it was difficult to ascertain whether a given death was self induced or was in fact due to misadventure. Cancer was regarded as a miscellaneous disorder, just as were rheumatic heart disease, cirrhosis of the liver, diabetes, the late effects of syphilis, postoperative deaths and the lymphomas or anemias, while subacute bacterial endocarditis was grouped with the unspecified infections. The results were expressed in percentage values of the causes of death for each series of groupings.

No attempt was made to analyze the cause of death of physicians over 60 years of age, for the diagnostic problems were almost invariably too complex. The appropriate classification of the cause of death of a physician over 70 years old reported to have succumbed to heart failure on an arteriosclerotic basis complicated by uremia from malignant disease of the bladder represents the type of riddle often encountered.

If one were interested solely in physicians who die, one would agree that vascular disease is now encountered very commonly as a cause of death among them at all ages and is increasing in frequency. Yet such a way of regarding the deaths of physicians is unsound, since no consideration is given to the number who are alive. In order to evaluate the data in a more comprehensive fashion and to give consideration to the numbers involved, an attempt was made to estimate what vital statisticians term specific death rates. According to Linder and Grove,[16] the specific death rate is a ratio the denominator of which represents the total number of deaths from any cause that could happen and the numerator the number that did happen. The specific death rate for each cause of death listed in table 2 and in each age group was obtained by the formula which they have advocated.

$$m = \frac{d}{p}k,$$

where

m = specific death rate for any defined cause
d = deaths occurring to persons in a defined group from a defined cause within a stated time
p = population in the defined group exposed to the risk of death from the defined cause within the stated time
k = a constant — 100,000 in the tables reported here

TABLE 2.—*The Common Causes of Death Among Physicians by Age Groups per Hundred Deaths in 1907, 1931 and 1942*

	Under 40						40 to 49						50 to 59					
	1907 and Surrounding Years		1931 and Surrounding Years		1942 and Surrounding Years		1907 and Surrounding Years		1931 and Surrounding Years		1942 and Surrounding Years		1907 and Surrounding Years		1931 and Surrounding Years		1942 and Surrounding Years	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Total number analyzed	493	100	290	100	356	100	382	100	250	100	332	100	467	100	581	100	353	100
Accidents	104	21	65	22	105	29	47	12	40	16	25	7	44	9	43	8	17	5
Pneumonia	72	15	45	16	27	8	46	12	36	15	19	6	45	10	38	7	16	4
Tuberculosis	62	12	29	10	12	3	17	5	10	4	11	3	14	3	12	2	6	2
Typhoid	49	10	0	0	0	0	12	3	0	0	0	0	7	1	1	0	1	0
Appendicitis	24	5	14	5	3	1	12	4	3	1	2	1	9	2	11	2	2	.5
Other infections	37	8	46	16	24	7	23	6	21	8	7	2	22	5	24	4	2	.5
Miscellaneous	68	14	37	13	77	22	89	23	40	16	86	26	93	20	114	19	60	17
Heart disease	46	9	39	13	73	20	69	18	73	29	145	44	115	25	248	43	198	56
Renal disease	22	4	9	3	15	4	43	11	7	3	11	3	53	11	20	3	6	2
Cerebral hemorrhage and thrombosis	9	2	6	2	20	6	24	6	20	8	26	8	65	14	70	12	45	13
All cardiovascular-renal diseases	77	15	54	18	108	30	136	35	100	40	182	55	233	50	338	58	249	71

13. Herrick, J. B.: Clinical Features of Sudden Obstruction of the Coronary Arteries, J. A. M. A. **59**: 2015-2020 (Dec. 7) 1912.

14. Epstein, A. A.: The Nature and Treatment of Chronic Parenchymatous Nephritis (Nephrosis), J. A. M. A. **69**:444-447 (Aug. 11) 1917.

15. Christian, H. A.: The Mechanism of Edema, J. A. M. A. **97**:296-299 (Aug.1) 1931.

16. Linder, F. E., and Grove, R. D.: Vital Statistics Rates in the United States 1900-1940, United States Department of Commerce, Bureau of the Census, 1943.

In using this formula the number of deaths from any cause for any of the years or age groups considered was estimated by applying to the total deaths for the year and to the age group under consideration the percentage values of each of the causes of death that had been listed. The

TABLE 3.—*Calculation of Specific Death Rate from Different Causes per Hundred Thousand Physicians Less Than Forty Years Old for Year 1907*

Cause	Number in Series	Percentage of Cases	Total Deaths for Year	Specific Death Rate per 100,000 for Each Cause Listed
Total cases	493	100	338	564
Accidents	104	21	71	119
Pneumonia	72	15	51	85
Tuberculosis	62	12	40	67
Typhoid	49	10	34	57
Appendicitis	24	5	17	28
Other infections	37	8	27	45
Miscellaneous	68	14	47	78
All cardiovascular-renal diseases	77	15	51	85

There has been a satisfactory diminution in the relative number of deaths from all causes and among all ages, especially notable among those under 40 but perceptible among those over 60. This statement merely reiterates that, as fewer younger physicians die each year, it is inevitable there should be more deaths among those who are older.

Almost any historian, in glancing backward, would say that since 1907 the jugulation of typhoid fever, the suppression of tuberculosis and syphilis, improvements in preoperative and postoperative care, the development of new surgical technics and the discovery of chemotherapeutic agents like the sulfonamide drugs and penicillin are among the more conspicuous milestones. As each one has been passed, physicians as well as their patients have benefited.

In 1907, typhoid, next to pneumonia and tuberculosis, was the illness most often fatal to begin-

TABLE 4.—*Common Causes of Death Among Physicians by Age Groups per Hundred Thousand in 1907, 1931 and 1942 (Specific Death Rate)*

Cause	Under 40			40 to 49			50 to 59			60 and Over		
	1907	1931	1942	1907	1931	1942	1907	1931	1942	1907	1931	1942
All causes	564	247	195	809	709	493	1,880	1,875	1,673	6,838	6,770	6,380
Accidents	119	55	57	98	114	34	169	151	85			
Pneumonia	85	39	15	98	106	29	191	131	66			
Tuberculosis	67	25	6	39	28	13	55	38	33			
Typhoid	57	0	0	23	0	0	16	0	0			
Appendicitis	28	12	1	33	8	5	37	38	9			
Other infections	45	39	14	49	56	10	92	76	9			
Miscellaneous	78	32	43	184	114	122	371	358	284			
Heart disease	50	32	39	148	205	215	480	800	989			
Renal disease	23	7	8	88	22	15	207	55	33			
Cerebral hemorrhage and thrombosis	12	5	12	49	56	40	202	228	215			
All cardiovascular-renal diseases	85	44	59	285	283	270	949	1,088	1,187			

figures in table 1 were used for the population figures of the different groups.

As an example of the manner in which these problems in arithmetic were actually solved, consider the year 1907 and the deaths among physicians who were 40 years old and less. In that year and age group there were 59,880 physicians alive, of whom 338 died. By applying the percentage figures of the common causes of death of men in that age group at about that time to these 338 deaths, each was accounted for in a fashion designed to illustrate the average picture of the times, and thereafter population figures were applied according to Linder and Grove's formula.

This method of using the figures was employed throughout, and a tabulation was made by which the specific death rate from common causes among physicians at different ages and times were compared.

The table summarizes in diagrammatic form much of the progress of medicine for the last thirty-five years as it affects the profession. ning practitioners. Now there is no typhoid. Pneumonia, next to misadventure, was the most frequent cause of death to the young, and it caused older physicians as well to slip out of the world with great regularity. First came antipneumococcus serum and next sulfonamide compounds and penicillin, so that now this disease is much less threatening.

Relatively speaking, there are fewer fatal accidents than there were. Trains, bad roads, poor lighting and the horse and buggy actually were more dangerous to physicians than are automobiles and airplanes. Syphilis also probably played a part in making life hazardous. At least there were many more persons, both within and without the ranks of the medical profession, who were abnormally irascible, so that many more physicians were killed in those times than now; and there were a number of deaths from late syphilis, which now are no longer encountered.

The effect of advances in surgery is suggested by the figures for appendicitis. The treatment of

appendicitis has improved steadily, so that now this disease is of little danger to physicians. In 1907, or about that time, a number of deaths were reported concerning which no other information was given than that they followed an unspecified type of operation. At present, postoperative deaths from any cause are reported much less frequently.

Tuberculosis has been fought steadily. Among younger physicians, relatively, it is much less serious than it was, indicating at least that the careful search for it during the last few years which has been made among medical students has yielded results. Other infections, like cerebrospinal meningitis or erysipelas to mention two striking examples, have come under control recently. On the whole, it is plain that the lives of many physicians are now being saved each year which hitherto were lost.

The deaths from vascular disease are of particular interest. The specific death rates from chosen because an overwhelming majority of physicians are white, are men and are above this age limit. Linder and Grove have divided the population into ages of 25 to 34, 35 to 44 and so on. Therefore, interpolations were adopted to make their age classification coincide with the one established here. The interpolations were as simple as possible: to compare with the figures for physicians who were under 40, all of the figures for the 25 to 34 age group of Linder and Grove were used and one half of those of the 35 to 44 group; and to compare with those for the 40 to 49 age group of physicians, half of the figures in the 35 to 44 group and half of those in the 45 to 54 group of Linder and Grove were employed. Similar calculations were used in the 50 to 59 year group, and, finally, to compare with the figures for physicians 60 years old and over, half of those of Linder and Grove for 55 to 64 were used and all their figures for ensuing ages. This method, as Emerson [17] pointed out, is not

TABLE 5.—*Death Rates from Certain Causes per Hundred Thousand Physicians in 1942 and in White Men More Than Twenty-Five Years Old in 1940 (Specific Death Rate)*

Cause	Under 40		40 to 49		50 to 59		60 and Over	
	Physicians	White Men	Physicians	White Men	Physicians	White Men	Physicians	White Men
All causes	195	535	493	723	1,673	1,830	6,380	5,800
Accidents	57	128	34	99	85	131		
Pneumonia	15	26	29	40	66	80		
Tuberculosis	6	70	13	71	33	93		
Heart disease	39	80	215	167	939	578		
Renal disease	8	20	15	42	33	117		
Cerebral hemorrhage and thrombosis	12	12	40	38	215	130		
All cardiovascular-renal diseases	59	112	270	247	1,187	825		

renal disease and cerebral hemorrhage or thrombosis appear to be diminishing in each age group, while those from heart disease among physicians over 40 are increasing. Possibly the emasculation of certain acute infections has diminished the incidence of glomerulonephritis, though it seems more probable that this apparent trend is due to nothing more significant than variation in terminology. The basic pathologic factor in almost all the cases within these three groups is vascular disease. If they are considered as a single unit and as one disease, their specific death rate in the different age groups and at different times has remained remarkably constant.

Physicians differ little from the rest of the citizens of the United States in respect to the causes of their deaths at different ages. Linder and Grove have constructed a table giving the specific death rates of the country for eight leading causes in 1940, from which certain comparisons can be made with the figures of 1942 concerning physicians. In this comparison the figures for white men above the age of 25 from Linder and Grove were used. This group was accurate, though the errors introduced probably do not affect the results.

The data in the table so constructed suggest that physicians up to the age of 60 are somewhat protected as a class; considerably fewer of them, for example, die of accidents and tuberculosis than of their controls, and their specific death rate from all causes is lower. On the other hand, their death rate from heart disease for persons over 40 is higher. This higher rate, however, is partially compensated for by their lessened liability to renal disease. Physicians past 50 appear to have proportionately more fatal cerebral vascular accidents than do members of the nonmedical population and a slightly higher death rate from all causes than have men in other occupations. Emerson and Hughes [18] reported similar conclusions in 1926.

17. Emerson, H.: Personal communication to the author.

18. Emerson, H., and Hughes, H. E.: Death Rates of Male White Physicians in the United States by Age and Cause, Am. J. Pub. Health **16**:1088-1093 (Nov.) 1926.

If, once again, deaths from heart disease, renal disease and cerebral vascular disease are grouped together, physicians between 40 and 60 years of age appear to die a little more commonly from these causes than do members of the general white male population, probably because they have a better chance of avoiding death from other insults. The differences at best are so slight as to be scarcely outside the limits of error entailed in the calculations.

In brief, there is nothing to prove that there has developed in the medical profession an ominous liability to coronary thrombosis or to any other manifestation of vascular disease. Nor has evidence yet developed to suggest that the danger to older physicians of overwork in wartime is much more than a bugbear. The viewpoint of Riesman and Harris and of Chadwick is sound: The increasing number of deaths among physicians each year from vascular disease is the price of medical advancement. So long as physicians continue to improve their methods and to build up a profession whose members grow steadily older in years and larger in numbers, the mortality from vascular disease will increase.

Roger Lee [19] has written an essay which all physicians should read. Speaking of vascular disease in general, he said that at the moment there is no method or clue for lessening its mortality. He went on to suggest, as did Osler [20] before him, that worry rather than hard work is the more baneful influence in life. In order to pass old age as gracefully as possible, he advised his readers at all costs to maintain some sort of objective in life lest lacking this they literally curl up and die. When all is said and done, can any hard working practitioner, as an end to his career, ask for a fate more honorable than, like Phrontes in the Odyssey, to be struck suddenly by the gentle darts of Apollo and to be dropped dead with the steering oar of the moving ship within his hands?

19. Lee, R. I.: Geriatrics: The Medical Care of the Elderly, New England J. Med. **230**:190-193 (Feb. 17) 1944.

20. Osler, W.: Aequanimitas, ed. 3, Philadelphia, P. Blakiston's Son & Co., 1932.

ABSENCE OF ELECTROCARDIOGRAPHIC CHANGES IN TSUTSUGAMUSHI FEVER (SCRUB TYPHUS)

REPORT OF TWO HUNDRED CONSECUTIVE CASES

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Observers of the tsutsugamushi fever (scrub typhus) which occurred in our Armed Forces early in the New Guinea Campaign, noted perivascular and interstitial infiltration of the myocardium with inflammatory cells plus changes in the muscle fibers of a varying degree.[1] Weakness and tachycardia were not uncommon in soldiers convalescent from the more severe infections. Because of these observations, the impression has been gained that residual cardiac damage might follow tsutsugamushi fever.

TABLE 1.—*Time of Obtaining Electrocardiogram*

	Number	Per Cent
During acute stage	10	5
1 to 4 weeks convalescent	184	92
6 to 12 months convalescent	6	3

The present study was undertaken to determine the possibility of electrocardiographic evidence of residual myocardial damage. Tracings were obtained for 200 consecutive patients admitted to a station hospital between May 23 and Sept. 1, 1944. Patients were seen at varying intervals following the onset of the disease. It will be seen in table 1 that 184 (92 per cent) of the group were examined within one to four weeks after the acute symptoms had subsided. Tracings were obtained for 10 patients during the height of the disease, while 6 others were examined six to twelve months after their illness. All were men.

Ninety per cent acquired their infection while in one of four of the highly endemic areas in New Guinea. The distribution of these is seen in table 2.

Of the recent convalescent group, 48 per cent showed evidence of eschars, 89 per cent still had some degree of adenopathy and all gave a history of a sustained febrile illness of seven to twenty-four days' duration. The blood serum of 50 per cent of the group still produced agglutination of Bacillus proteus Kingsbury strain in dilution of 1 : 160 or higher.

ELECTROCARDIOGRAPHIC OBSERVATIONS

In no instance was there an abnormal pattern which could be attributed to the disease. The original tracing taken for 1 patient showed the diphasic T wave in lead I and inverted T waves in leads II, III and IV F. A short QT interval caused a digitalis effect to be suspected.[2] Investigation revealed that this man had received 14 cat units of digifolin intramuscularly ten days previously. An electrocardiogram taken after a lapse of two weeks showed upright T waves in the limb leads; there was a shallow inversion of the T wave in lead IV and the QT interval had returned to normal.[3]

Isolated deviations from the normal, based on the standards of the Criteria Committee of the New York Heart Association in 1939, occurred in 44 per cent of the patients. This value is comparable to that observed by Viscidi and Geiger in their study of 486 adults between the ages of 18 and 38.[4] In none of their cases was there a history of acute rheumatic fever or objective evidence of cardiac disease. Using the same criteria, they found isolated deviations from

TABLE 2.—*Area in Which Infection Was Acquired*

Area	Per Cent
I	27
II	25.5
III	17.5
IV	17.5
Others	10

1. Corbett, A. J.: Scrub Typhus, Bull. U. S. Army M. Dept., November 1943, no. 70, pp. 34-54. Lipman, B. L.; Byron, R. A., and Casey, A. V.: Clinical Survey of Scrub Typhus Fever, ibid., January 1944, no. 72, pp. 63-70.

2. The value of K in Bassett's formula,

$$K = \frac{QT}{\sqrt{\text{cycle length}}},$$

was 0.342 as compared with the normal of 0.392.

3. The value of K became 0.400.

4. Viscidi, P. C., and Geiger, A. J.: Electrocardiographic Observations on Five Hundred Unselected Adults at Work, Am. Heart J. **26**:763-768 (Dec.) 1943.

the normal in 48.8 per cent of their tracings. The incidence of the various types of isolated deviations from the normal occurring in their group as compared to this one is listed in table 3. It will be noted that they are in close agreement in most intsances. Delayed auriculoventricular conduction was present four times (0.8 per cent)

TABLE 3.—*Incidence of Deviations*

Criteria	Viscidi and Geiger's Series No.	%	This Series No.	%
Limb Leads				
P Wave				
Direction: Inverted in two leads	1	0.2	0	0
Amplitude: Largest P wave less than 0.5 or more than 2.5 mm	..	...	1	0.5
Duration: 0.12 second or more	1	0.2	1	0.5
PR Interval				
0.22 seconds or more	4	0.8	0	0
QRS Complex				
Duration: More than 0.10 second	2	0.4	0	0
Amplitude: Less than 5 mm. in lead with largest amplitude or sum of over-all dimension in the 3 leads less than 15 mm	9	1.8	5	2.5
Contour: Slurring in 2 or more leads.	126	25.2	52	26.0
Deep Q waves (exceeding 15%, 20% or 25% of largest QRS amplitude in leads I, II or III respectively)	8	1.6	0	0
Axis deviation: More than slight	5	1.0	0	0
RS-T Junction				
Deviation from isoelectric level of more than ± 1 mm	6	1.2	3	1.5
T Wave				
Abnormal direction or amplitude	19	3.8	12	6
Q-T Duration				
The value of K in formula K = QT/ √cycle length exceeds normal of 0.392	85	17	31	15.5
Pericordial Lead IV F				
P Wave				
Direction: Inverted more than 0.5 mm.	35	7	2	1
Amplitude: Greater than 1.5 mm	2	0.4	0	0
QRS Complex				
Amplitude: Over-all dimension less than 8 mm	80	16	7	3.5
R Wave: Less than 3 mm	4	0.8	5	2.5
Q Wave: More than 3 mm	2	0.4	0	0
RS-T Junction				
Deviation from isoelectric level or more than −0.6 mm. or +2.0 mm	0	0	0	0
T Wave				
Abnormal direction or amplitude	19	3.8	3	1.5

and delayed intraventricular conduction occurred twice (0.4 per cent) in their group, whereas neither occurred in this series. Deep Q waves occurred eight times (1.6 per cent) in their group but did not appear in this series. Abnormalities in the direction and amplitude of T waves was slightly less common in the limb leads (3.8 per cent as against 6.0 per cent) but slightly more common in the precordial lead (3.8 per cent as against 1.5 per cent) in their group as compared to this series. (Inversion of the T wave occurred only once in the typhus group.) Low voltage of the QRS complex in the precordial lead was four and one-half times as common (16 per cent as against 3.5 per cent) in their series as in this one. There was a slightly greater incidence of low R waves in the group with tsutsugamushi disease (2.5 per cent as against 0.8 per cent), but this may be explained by the fact that all tracings were taken with subject in the supine position. In no instance was the R wave in lead IV less than ± 1.0 mm.

COMMENT

The absence of conduction disturbances and abnormal changes in the T waves in the electrocardiograms of this study is significant. A similar absence would not be expected after acute rheumatic fever or diphtheria, acute infections known to affect the heart muscle. Typhoid and other acute infections produce inflammatory changes in the myocardium similar to those seen in tsutsugamushi fever, without leaving demonstrable residual myocardial damage. Tachycardia which sometimes follows tsutsugamushi fever may well be vasomotor in origin, as it is in other prolonged febrile illnesses.

SUMMARY AND CONCLUSION

1. An electrocardiographic study was made of 200 consecutive patients convalescent from tsutsugamushi (scrub typhus) fever.

2. No abnormal electrocardiographic patterns were found.

3. The incidence of isolated deviations from the normal was no higher than that found in the electrocardiograms of healthy persons of the same age.

Lieutenant Colonel Philip W. Brown, Medical Corps, Army of the United States, gave help and criticism in this study, and Sergeant Stephen E. Fedorcha, Medical Department, Army of the United States, supplied technical assistance.

SOUTH AMERICAN TRYPANOSOMIASIS (CHAGAS' DISEASE)

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The varied geographic areas in which American troops are stationed or operating in the present war are such as to expose them to a variety of diseases, some of which, though not rarities in the respective locales where infections may occur, are exotic if considered in the light of daily medical practice in the United States. Some of the diseases are of more serious consequence in the chronic stages than in the more acute periods and, unfortunately, more difficult to diagnose then. Many of the tropical protozoan diseases are of this character. It is a matter of no small consequence, therefore, that all physicians in the United States should have a wider knowledge of these and other tropical diseases than a mere acquaintance with their names. Clinical reports of the observations made by medical officers serving with American forces in the various theaters of operations will do much to acquaint American physicians with the more unusual diseases encountered among the troops and prepare the ground for more prompt recognition and treatment in the less obvious stages of development that may be encountered among some of them after return from foreign theaters. Needless to say, preventive measures to insure against spread of the diseases will also be more adequately anticipated and instituted.

It has been our privilege to make a diagnosis for, study and treat 2 American soldiers with South American trypanosomiasis, or Chagas' disease. Both were infected by the causative trypanosome in Panama, and both were observed during the acute stage of the disease. Although endemic cases of Chagas' disease have been recognized in nearly every American country from Mexico to Argentina, few reports and observations on the acute form of the disease in adults have been recorded in the American or English medical literature. From observations that have been previously made on the disease in Panama, it has been supposed that in this area the disease, particularly in adults, is not clinically distinctive.[1]

In these 2 men, however, the acute stage of the disease was manifested by clinically distinctive symptoms, and in the second patient the disease picture was of the same type as has been observed in Brazil, Argentina and other South and Central American countries. Because of these facts and in order to call attention to the cardiac manifestations that may be exhibited during the acute and the chronic phases of the illness, we are presenting our observations on the 2 patients and also a brief summary of the more recent literature on Chagas' disease.

Chagas' disease, or South American trypanosomiasis, is essentially and primarily a disease of animals. It was first recognized and studied as such by Chagas in 1907. In 1909 he first recognized the disease in man. Many species of small mammals have been found to be naturally infected, and many others have proved experimentally to be capable of infection. Not only may the naturally infected mammals, such as the armadillo, opossum, rat and bat, serve as reservoirs for the spread and transmission of the disease, but domesticated animals, such as the dog, cat or guinea pig, may also become links in the transmission to man.[1c, d]

The etiologic agent is a protozoan parasite, Trypanosoma cruzi, which invades the blood and tissues of man or other mammalian hosts. It is transmitted from animal to man and from animal to animal through the medium of an insect vector of the genus Triatoma. The insect is infected only through the medium of infected blood from some mammalian host; T. cruzi is not transferred from insect to insect.[2] The lar-

Owing to lack of space, this paper has been abbreviated for publication in THE ARCHIVES by omission of a number of the illustrations. The complete article will appear in the authors' reprints.

1. (*a*) Johnson, C. M., and Kelser, R. A.: The Incidence of Chagas' Disease in Panama as Determined by the Complement-Fixation Test, Am. J. Trop. Med. **17**: 385, 1937. (*b*) Johnson, C. M., and De Rivas, C. T.: Six New Cases of Chagas' Disease in Panama with a Review of Previous Cases, ibid. **16**:47, 1936. (*c*) Clark, H. C., and Dunn, L. H.: Experimental Studies on Chagas' Disease in Panama, ibid. **12**:49, 1932. (*d*) Johnson, C. M.: American Trypanosomiasis, M. Clin. North America **27**:822, 1943.

2. Strong, R. P.: Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases, Philadelphia, The Blakiston Company, 1942, vol 1, pp. 207-228.

val and nymphal forms may become infected and also serve as vectors. Experimental infections or at least harboring of the trypanosome has also been produced in other blood-sucking insects of the bedbug and tick families.[3]

Although the disease to date has been considered as one limited to South or Central American regions, it is to be remembered that it could become endemic in the United States. Naturally infected triatomas and ones capable of acting as vectors if infected have been found in the states of California, Texas, Arizona, New Mexico, Utah and Florida.[4] Johnson,[1d] however, has pointed out that only those triatomas which invade houses are of epidemiologic importance for the human disease. Clark [1c] has also pointed out that it, is usually only as a consequence of man's moving in and disturbing the natural triatoma-mammal, parasite-host relationship that he becomes a victim of the infection.

Most authorities believe that the trypanosome enters the blood and tissues of its host from contamination of the wound at the feeding site or of a wound on a mucous membrane surface, such as the conjunctiva of the eye, by trypanosomes in the fecal material deposited nearby by the insect vectors.[5] Thus the modus operandi of transmission is similar to that by which epidemic typhus is transmitted to man by the louse rather than to that by which the malarial plasmodium is introduced by the female anopheles mosquito.

3. Strong.[2] Johnson.[1d]

4. (*a*) Kofoid, C. A., and Whitaker, B. C.: Natural Infection of American Human Trypanosomiasis in Two Species of Cone-Nosed Bugs, Triatoma Protracta Uhler and Triatoma Uhleri Neiva, in the Western United States, J. Parasitol. **22**:259, 1939. Packchanian, A.: Natural Infection of Triatoma Gerslakeri with Trypanosoma Cruzi in Texas, Pub. Health Rep. **54**:1547, 1939. Wood, F. D., and Wood, S. F.: Present Knowledge of the Distribution of Trypanosoma Cruzi in Reservoir Animals and Vectors, Am. J. Trop. Med. **21**:335, 1941. Wood, S. F.: Notes on the Distribution and Habits of Reduviid Vectors of Chagas' Disease in the Southwestern United States, Pan Pacific Entomologist **17**:85, 1941. Wood, S. F.: Observations on Vectors of Chagas' Disease in the United States: II. Arizona, Am. J. Trop. Med. **23**:315, 1943. Packchanian, A.: Infectivity of the Texas Strain of Trypanosoma Cruzi to Man, ibid. **23**:309, 1943. (*b*) American Trypanosomiasis in Brazil, Foreign Letters, J. A. M. A. **121**:65 (Jan. 2) 1943.

5. (*a*) Brumpt, E.: Mode de transmission de la maladie de C. Chagas, Ann. de parasitol. **17**:320, 1939. (*b*) Denecke, K., and von Haller, E.: Recherches experimentales sur le mode de transmission et le cours de l'infection par Trypanosoma cruzi chez les souris, ibid. **17**:313, 1939. (*c*) Chagas, E.: L'infection experimentale chez l'homme par Schizotrypanum cruzi, Compt. rend. Soc. de biol. **118**:280, 1935. (*d*) de Andrade, C.: Chagas' Disease: Ocular Conjunctiva as Most Frequent Site of Infection, Arch. Ophth. **26**:341 (Sept.) 1941.

After a variable period in the blood stream, the trypanosome invades the parenchymal cells of some organ for which it has a predilection, in which it assumes the leishmanial form and multiplies by longitudinal splitting. Multiplication of the leishmanial form continues until the affected cells rupture and the parasites escape to reinvade the blood stream or other tissue cells.

The most frequent sites for invasion of tissue and proliferation by the parasites are the heart, brain and liver. The voluntary muscles, spleen, lymph nodes, adrenals, ovaries, testes, thyroid and skin have also been found to be invaded.

Johnson [6] has demonstrated that as long as the parasitized cells remain intact there is no cellular reaction. However, the rupture of the cell and the liberation of the parasites call forth an intense inflammatory reaction with infiltration of macrophages, lymphocytes and plasma cells in the interstitial and perivascular spaces. After the rupture of the affected cells, the lesion is healed by fibroblastic proliferation and scar tissue formation.

The clinical symptoms of Chagas' disease have been found to be varied, ranging from acute manifestations of the type associated with any severe febrile illness to symptoms so negligible as to pass unnoticed by the patient and even by the physician. Particularly has this lack of symptoms been noted in the disease as it has been previously observed among adults in Panama.[1] It is only during the acute stage of the disease that the clinical picture is diagnostic. In the chronic stages, the symptoms and signs exhibited are a reflection of the damage present in some organ, most often the heart.

In his earlier papers Chagas described in detail various forms of the disease, which he divided into five clinical types, namely, the pseudomyxedematous, the myxedematous, the cardiac, the nervous and the chronic form with subacute manifestations. He attributed these syndromes to involvement by the trypanosome of the heart and brain and of the thyroid, testes and other endocrine glands. In recent years, it has been conclusively demonstrated that such syndromes are not the result of infection with T. cruzi alone but are manifestations of other associated conditions, such as endemic goiter and cretinism, which diseases are frequently observed in certain of the areas where Chagas made his original observations.[7]

6. Johnson, C. M.: Cardiac Changes in Dogs Experimentally Infected with Trypanosoma Cruzi, Am. J. Trop. Med. **18**:197, 1938.

7. Lobo L., A.: Doenca de Chagas e bocio endemico, Brasil-med. **53**:1031, 1939. Johnson.[1d] Strong.[2] Footnote 4 *b*

In children and also at times in adults the infection is manifested as an acute febrile illness which varies considerably in severity, and in young persons it often terminates fatally. As a rule, the younger the patient, the more severe the symptoms. The incubation period is between seven and fourteen days, being ten to twelve days in experimentally infected human beings.[8] The fever may last from a few days to several weeks, with the temperature ranging to 104 F. or higher. There does not appear to be any specific type of temperature curve, but the fever is usually remittent or intermittent in type.[9]

A common early sign of the disease, sufficiently characteristic to be of diagnostic value, is the unilateral (occasionally bilateral) trypanosomal ophthalmia, which has been designated Romaña's sign. The swelling of the lids starts abruptly, extends outward to involve the neighboring tissue of the face and tends to disappear slowly. Painless edema, a reddish violet discoloration of the lids with conjunctival injection and, occasionally, chemosis are present. The cornea is not affected, and conjunctival secretion is scanty. The preauricular, parotid, submaxillary or cervical lymph nodes on the same side are frequently enlarged. Clinical cases often are characterized by this stubborn unilateral ophthalmia, which persists throughout the acute febrile stage of the disease. It is believed that the inflamed eye marks the site of inoculation of the infected material from the reduviid vector.[10] Experimentally it has been shown that human beings and animals can be infected by having the excreta of infected bugs placed on the conjunctiva.[11]

In cases of severe infection an extensive edema, involving not only the face but the extremities and even the whole body, has been described. It is said to be a hard edema of elastic consistency, which does not pit on pressure. Chagas believed that the edema was due to a myxedematous infiltration of the subcutaneous tissues resulting from the specific action of the parasite and its toxin on the thyroid gland, a view which is no longer tenable.[12] Transient edemas characteristic of the early stages of African trypanosomiasis are assumed to be due to a general toxic action of the parasite, and it is probable that the edema of the acute stage of Chagas' disease is a closely related phenomenon. There is little doubt that the edema observed in the chronic stage marked by severe myocardial damage is simply a result of cardiac decompensation.

In some cases, the clinical signs and symptoms of meningoencephalitis are the predominating observations. These cases are almost uniformly fatal. The brain and meninges, when involved, are congested and edematous, with numerous small inflammatory foci scattered throughout the brain substance. On section, these lesions are found to consist of collections of neuroglia and mononuclear cells. These foci are not related to the blood vessels and occur in all parts of the brain. Parasites may be found in the spinal fluid, in the neuroglia and in the large mononuclear cells of these inflammatory foci.

Because of the apparent predilection of T. cruzi for the myocardium, cardiac symptoms are frequent accompaniments of the disease. In general, the cardiac manifestations of the acute stage are ill defined and may be indicated solely by the distant quality of the heart sounds, tachycardia and definitely irregular rate and rhythm. The acute stage lasts from four to eight weeks; and, in those patients who survive, the temperature returns to normal; trypanosomes disappear from the blood, and the edema and other signs of disease disappear. Occasionally the acute stage is prolonged for months. E. Chagas[13] stated the belief that in the absence of reinfection the disease may die out, while C. Chagas and others have stated that spontaneous cure does not occur and that those who escape death go on into the chronic stage of the disease.[14]

At death, in the acute stage of the disease, the heart is usually found to be enlarged and often shows a yellowish mottling of the myocardium. Occasionally the pericardial sac contains an excess of fluid of a greenish or yellowish green color, sometimes containing a few fibrinous flakes. According to Chagas, cardiac enlargement is due primarily to dilatation, with little or no myocardial hypertrophy.[15] Microscopically, an intense myocarditis with parenchymatous degeneration and an associated infiltration of the interstitial tissues by lymphocytes, plasma cells, round cells and macrophages is observed. The muscle fibers are widely sepa-

8. Strong.[2] Chagas.[5e]

9. Mazza, S., and others: Investigaciones sobre la enfermedad de Chagas, Publication 43, Universidad de Buenos Aires, Mision le estudios de patología regional argentina, Buenos Aires, Universidad de Buenos Aires, 1940; Publications 46 and 51-53. Johnson.[1d] Strong.[2]

10. Chagas, E., and Dias, E.: Romana Sign, Hospital, Rio de Janeiro **19**:185, 1941.

11. Johnson.[1d] Footnote 5.

12. Yorke, W.: Chagas Disease: A Critical Review, Trop. Dis. Bull. **34**:275, 1937. Johnson.[1d] Strong.[2] Footnote 4 *b*.

13. Chagas, E.: Summula dos conhecimantos actuaes sobre a Trypanosomiase Americana, Mem. Inst. Oswaldo Cruz **30**:387, 1935.

14. Johnson.[1d] Strong.[2] Yorke.[12]

15. Chagas, C.: A forma cardiaca da Trypanosomiase Americana, Arch. brasil. de med. **18**:46, 1929.

rated from one another, and some show fragmentation and hyaline degeneration. Large nests of the leishmanial form of the parasites may be found either in the muscle fibers themselves or in large mononuclear cells lying between the muscle fibers. If the parasitized fibers remain intact, there is no cellular reaction around them or edematous separation. It is only after rupture and liberation of the parasites that the characteristic intense inflammatory reaction occurs.[6] The epicardium and endocardium likewise often show signs of cellular infiltration and of nests of parasites.

If the disease progresses, cardiac symptoms become more manifest. The patient may complain of easy fatigability, palpitation, faintness, vertigo, exertional dyspnea, vague precordial pains and a sense of constriction in the chest. Occasional radiation of pain to the neck has been described. The more common physical signs are cardiac enlargement, edema, fall of blood pressure and cardiac arrhythmias. Clinical and roentgenologic examination may reveal cardiac enlargement, usually involving both ventricles but especially the left. This enlargement may progress with the disease and reach the degree of a cor bovinum.

The changes that occur in cases characterized by chronic cardiac disturbances are less well known. E. Chagas stated [15] that the chronic form of the disease reveals hyperplasia of the connective tissue, with fibrosis and parenchymatous degeneration. He stated that the parasites tend to migrate to neighboring regions, so that, adjacent to fibrotic areas, acute lesions characterized by inflammatory cellular exudate, degenerative muscle fibers and occasional parasitized cells are to be found.

Arrhythmias constitute a most important feature of the cardiac picture. These have been attributed to the localization of the parasite in the musculature of the heart, which either interferes with the conductivity or increases the excitability of the muscle.

The most intensive pathologic changes in the heart have been found in experimental animals to be in the cardiac muscle adjacent to the epicardium and endocardium, particularly severe at the base of the heart and near the auriculoventricular junction.[6] Chagas and Villela [16] have described the following cardiac arrhythmias: sinus tachycardia and bradycardia, premature systoles of ventricular, auricular and nodal origin, all stages of auriculoventricular block from prolonged auriculoventricular conduction to complete auriculoventricular block, auricular fibrillation and flutter, paroxysmal tachycardia and alternans of the heart. Changes in rhythm may occur from day to day. The associated clinical manifestations do not differ from those associated with other cardiopathies. Low voltage of the QRS complexes and flattening of the P and T waves have also been described. With cardiac decompensation the symptoms and signs of pulmonary and systemic engorgement occur. The prognosis of the cardiac form of the disease is poor. Sudden death is common, especially in cases of heart block and ventricular arrhythmias. E. Chagas [17] reported a sudden fatal outcome in 27 out of 35 cases of Chagas' disease.

The frequency of occurrence of chronic myocardial disease in areas where human infection with T. cruzi is known to occur has led Yorke and others to believe that South American trypanosomiasis is responsible for many of these cases.[18] Some think the chronic cardiac form of the disease to be a sequel of acute infection in childhood; others, that it is a consequence of repeated infection in later life.[19]

The appearance of cutaneous eruptions as a manifestation of the acute stage of the disease has not been generally appreciated until recent years. Clark first reported this as a manifestation of the disease in 1932,[1c] but his observation appears to have gone by unappreciated until clinical and pathologic descriptions of cutaneous lesions were called attention to by Mazza and his collaborators in 1940.[9] Mazza has classified the lesions into two large groups: first, "chagomas" and, second, "schizotrypanomides." The latter he considers true exanthems.[9]

The first is a nodular and/or ulcerative granulomatous type of lesion occurring at the primary site of invasion by the parasite. The histopathologic description is similar to that of any granulomatous process with tuberculoid formation, with giant cells similar to the Langhans type and with lymphocytic and mononuclear infiltration. The one distinguishing feature is the demonstration of the leishmanial forms of the parasites in the large mononuclear cells found abundantly in the subepidermal layers and

16. Chagas, C., and Villela, E.: Forma cardiaca da Trypanosomiase americana, Mem. Inst. Oswaldo Cruz **14**:5, 1922.

17. Chagas, E.: Estudio electro-cardiographico na forma cardiaca da Trypanosomiase americana, Folha med. **2**:97, 1930.

18. (*a*) Mazza, S.; Basso, R., and Jong, M. E.: Investigaciones sobre la enfermedad de Chagas: I. Primer caso mortal de forma cronica cardiaca de enfermedad de Chagas, comprobado en Mendoza, Publication 42, Universidad de Buenos Aires, Misión de estudios de patología regional argentina, Buenos Aires, Universidad de Buenos Aires, 1939, p. 3. (*b*) Johnson.[1d] Strong.[2] Footnote 4 *b*. Mazza and others.[9] Yorke.[12]

19. Footnote 4 *b*. Yorke.[12] Mazza, Basso and Jong.[18a]

about the lymphatic spaces. He describes these lesions as arising at the primary site of inoculation ("chagomas of inoculation") and also as occurring during the course of the disease at other cutaneous sites ("chagomas due to hematogenous spread"). In reading the clinical and histopathologic description of the "chagomas" recorded by Mazza, we were particularly impressed by the similarity between these lesions and the ones we have observed in cases of South American cutaneous leishmaniasis. Mazza particularly stressed the great similarity between the "chagomas" and the granulomatous lesions of sporotrichosis. Johnson [20a] has also noted the similarity between cutaneous South American leishmaniasis and sporotrichosis and in 1939 made a brief mention of it. This similarity is a point of some significance in differential diagnosis and one not widely appreciated as yet in articles or textbooks dealing with these diseases.

The cutaneous lesions of the second group are histologically indistinguishable from the common exanthems, such as roseola or rubella. Mazza [9] expressed the opinion that much of the inflammatory reaction seen in these lesions is due to an explosive type of local tissue allergy, which is set off by the lodgment of a few of the parasites in a skin that for some reason has become sensitized to the organism. It is a type of reaction much like that seen in some of the other "ids."

The "schizotrypanomides" occur only after the disease has become systemic. Three clinical types have been observed: the morbilliform, the urticarial and the erythematous, maculopapular eruptions.

The morbilliform type of reaction strongly resembles that of roseola or rubella and appears on or about the fifteenth day of the illness, usually after Romaña's sign has become fully developed. Urticarial lesions have also been observed at about this time. The third type, which is described as comprising multiple, discrete maculopapular erythematous blanching eruptions of varying size, appears between the fifth and twenty-fourth day of the disease, usually on the anterior surface of the chest, upper part of the abdomen or extensor surfaces of the arms and thighs. The face, palms, soles and mucous membranes are not involved.

Hepatomegaly is often observed. On pathologic study, the organ reveals parenchymatous changes with fatty degeneration. The presence of the parasite in the parenchymal cells and Kupffer cells has been recognized.

The spleen may be somewhat enlarged and appears congested. The preauricular and cervical lymph nodes are often enlarged, and histologic examination reveals congestion, lymphoid hyperplasia, mononuclear cell production and phagocytosis.

Other symptoms which may be encountered from time to time depend on the visceral site of invasion by the parasite. Thus, myalgic pain, testicular pain or swelling and adrenal insufficiency are among those that have been reported.

Histologic changes of the general character previously described have been observed in the thyroid, adrenals, ovaries and testes of patients who died in the acute stages of the disease.

The changes that occur in the skeletal muscles are essentially similar to those that occur in the heart. Between the muscle fibers are small foci of cellular infiltration, and parasites may be found both within the muscle fibers and in large mononuclear cells lying between them.

Often the symptoms and physical signs just outlined are so clearcut and distinctive as to justify a clinical diagnosis of Chagas' disease on these grounds alone. In other instances laboratory proof will be necessary. In all instances laboratory confirmation should be sought.

Confirmatory diagnosis of the disease is directed toward either actually demonstrating the parasite or obtaining satisfactory evidence of its presence in the host by serologic methods. In the acute stages, the simple microscopic examination of fresh cover slip preparations or of stained thick blood films may suffice to disclose the presence of the trypanosome. Thick drop preparations of blood are usually necessary because of the scarcity of parasites circulating in the peripheral blood. When the parasites are too scanty to be detected in this way, inoculation of 5 to 10 cc. of the suspected blood into guinea pigs or puppies and examination of the blood after two weeks may allow one to demonstrate the parasite. Killing the animals after a few more weeks often permits one to demonstrate the parasite in the cardiac muscles or other tissues on histologic examination. Another method of demonstrating T. cruzi in the peripheral blood is that to which Brumpt [21] gave the name "xenodiagnosis." It consists in allowing laboratory-bred, known uninfected triatomes to feed on the patient suspected of having the disease and in ascertaining after about two weeks

20. (*a*) Johnson, C. M.: Personal communication to the authors. (*b*) Clark, H. C.: Annual Report of the Gorgas Memorial Laboratory, 1939, House Document no. 543, 76th Congress, 3rd Session, Washington, D. C., Government Printing Office, 1940, p. 11.

21. Brumpt, E.: Le xenodiagnostic: Application au diagnostic de quelques infections parasitaries et particulier a la trypanosomose de Chages, Bull. Soc. path. exot. **7**:706, 1914.

whether the intestinal tract of the insect contains the parasites.

A more efficient test for the presence of Chagas' disease is the complement fixation test of Guerreiro and Machado.[22] These investigators found a glycerin and water extract of the heart and spleen of heavily infected puppies to be a highly specific antigen. In 1936, Kelser [23] described a modification of this test in which artificial cultures of T. cruzi were used as an antigen. Romana and Dias [24] have recently reported a further modification of the test. They used an alcoholic antigen of the cultured forms instead of the glycerin–saline solution antigen of Kelser.

goencephalitis, on biopsy of infected muscle and in cutaneous lesions. Other nonspecific laboratory observations which have been stressed by Mazza [9] are the pronounced degree of lymphocytosis which persists throughout the acute stage of the disease and the increase of eosinophils toward the latter part of the acute illness.

A progressive hypochromic anemia has been noted in some instances, particularly among children.

REPORT OF CASES

CASE 1.—A white American soldier, aged 29, was admitted to an army station hospital in Panama on Dec. 15, 1942, for observation for possible intracranial injury after a fight with another soldier. Except for a mild headache, he was symptom free at the time of admission. He had been stationed at various posts on both the Atlantic and Pacific sides of the Isthmus in the preceding two months and had been assigned to a recently cleared jungle position for a week prior to his admission to the hospital. He gave no history of any recent insect bites. Except for an attack of malaria in May 1942 and acute gonorrhea in September 1942, his general health had been excellent. His past history was otherwise not contributory.

Examination on his entry revealed a well developed and well nourished man who did not appear acutely ill. The temperature was 99.5 F. and the pulse rate 100

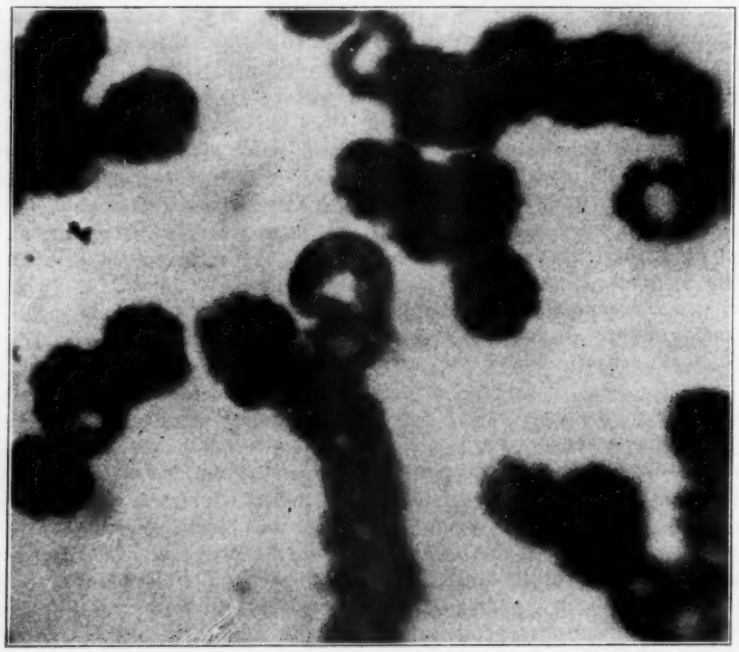

Fig. 2 (case 1).—Photomicrograph of T. cruzi as identified in thin blood smear. Note the characteristic C-shaped form in which the parasite appears. The nucleus is in the central portion. The large oval kinetoplast is situated posteriorly. At this magnification the kinetoplast is seen to consist of two bodies. The larger, more proximally placed, body is the parabasal body. The smaller body, situated in the posterior end of the parasite, from which the flagellum arises is the blepharoplast. These are the distinguishing identifying features of T. cruzi in its trypanosomal form, as found in the circulating blood.

T. cruzi has in some instances been demonstrated in the spinal fluid of patients with menin-

22. Guerreiro, C., and Machado, A.: Da reaccao de Bordet e Gengou no molestia de Carlos Chagas como elemento diagnostico, Brasil-med. **27**:225, 1913.

23. Kelser, R. A.: A Complement-Fixation Test for Chagas Disease Employing an Artificial Culture Antigen, Am. J. Trop. Med. **16**:405, 1936.

24. Romana, C., and Dias, E.: Recao de fixacao do complemento na Doenca de Chages, com antigeno alcoolico de cultura do "Schizotrypanum cruzi," Mem. Inst. Oswaldo Cruz **37**:1, 1942.

per minute. A mild seborrhea of the scalp and face, several superficial abrasions about the face and some mildly contused areas on the trunk were noted. The eyes, ears, nose and throat were essentially normal. The thyroid gland was not palpably enlarged at the time of the initial or subsequent examinations. The lungs were found to be clear on percussion and auscultation. The heart was not enlarged, and the rhythm was regular. A soft systolic murmur was heard over the apex. The blood pressure was 100 mm. of mercury systolic and 70 mm. diastolic. On abdominal examination, the tip of the spleen could be felt below the left costal margin. It was firm and nontender.

Course in Hospital.—On the fifth day in the hospital, the patient had a chill, with a subsequent rise of temperature to 104.5 F. Physical examination at that time revealed nothing abnormal except the previously mentioned palpable spleen. A blood smear was positive for Plasmodium vivax on this day, and quinine therapy was started. The therapeutic response was prompt. Two days later, he began to complain of generalized muscular aching and severe pain in the knee joints and in the fingers of both hands. There was no clinical evidence of an inflammatory reaction in any of the joints at this time. In spite of adequate doses of quinine sulfate and quinacrine hydrochloride, the patient continued to have a daily remittent fever. Several cultures of the blood showed no growth, and repeated malaria smears were now negative for causative organisms.

On the twelfth day in the hospital an area of redness was noted about the nose and malar eminences. The next day, the right malar eminence appeared swollen. This area was not tender and did not pit on pressure. It gave a sensation to the palpating finger of firm induration of the subcutaneous tissues. The posterior cervical lymph nodes were moderately enlarged bilaterally. The inflammatory hyperemia subsided with the local use of hot compresses and the oral administration of sulfathiazole, but the fever and swelling persisted. This induration gradually subsided during the next three weeks. On the eighteenth hospital day, three days after administration of sulfathiozole had been discontinued, the proximal interphalangeal joint of the left middle finger became red, hot, swollen and tender. At this time, Capt. James R. Schmidt, the hospital pathologist, reported the presence of T. cruzi in one of the blood films (fig. 2).

In view of the lack of any recognized specific therapy for this disease and because of the pathologic evidence that the leishmanial form of the parasite is the one that produces the damage, it was felt that an antimony preparation should, at least theoretically, prove of some benefit. On Jan. 10, 1943, his twenty-seventh day in the hospital, administration of an antimony preparation was started; 3 cc. of fuadin was given intramuscularly. As to whether the drug was of any specific benefit to the patient or not is speculative, but improvement was promptly noted, and his fever began to subside. He received 13 cc. of fuadin intramuscularly during the next ten days, and, in all, 33 cc. was given over a period of forty-seven days. All of his symptoms disappeared during this period, and he made an uneventful recovery. He at no time showed evidence of cardiac damage and was discharged to full duty status on his ninety-fourth day in the hospital.

Clinical laboratory studies showed the patient to have a moderate anemia of a hypochromic type, which responded satisfactorily to iron and dietary measures. He was also observed to have a lymphocytosis and an elevated sedimentation rate. The significant hematologic findings we have summarized in table 1. The reaction to a complement fixation test (Johnson and Kelser modifications of the Guerriro and Machado test), performed for us by Dr. Johnson, of the Gorgas Memorial Laboratory, was reported as negative.

TABLE 1.—*Results of Hematologic Examinations (Case 1)*

Date	Red Blood Cells	Hemoglobin	White Blood Cells	Polymorphonuclears Leukocytes	Lymphocytes	Eosinophils	Mononuclear Leukocytes	Blood Sedimentation Rate, Mm.	Comment *
December 19	.....	80	5,650	..	..	..	..	..	Smear: positive for Plasmodium vivax
December 28	3,400,000	74	11,250	77	21	2	..	96	Smear: negative for P. vivax
December 30	3,050,000	80	5,500	68	30	2	..	..	Smear: negative for P. vivax
January 3	.....	..	.....	..	..	..	..	..	Icterus index 10. smear: positive for Trypanosoma cruzi
January 9	3,800,000	83	8,300	68	28	4	..	89	Plate.et count 165,000; bleeding time 4½ minutes; clotting time 3¾ minutes
January 14	3,500,000	80	6,350	68	30	2	..	..	Total protein 7.7 Gm.
January 21	4,450,000	80	8,000	66	33	1	..	..	
January 29	.....	..	5,400	49	43	8	..	52	
February 7	.....	..	.....	..	..	..	..	24	
February 14	.....	..	5,650	35	62	2	1	15	
February 22	.....	..	5,400	59	41	..	..	..	
March 1	4,510,000	85	.....	..	..	..	..	..	
March 8	.....	90	4,700	44	49	6	1	..	

* The reactions to the Takata-Ara and Napier's serum tests were negative, and the total serum protein was not increased.

Roentgenograms revealed clear pulmonary fields and a normal cardiac silhouette.

An electrocardiogram taken January 11 revealed a sinus mechanism with a rate of 93 per minute and a conduction time of 0.16 second. The QRS complexes measured 0.08 second. The T waves were upright and normal in all the leads. A second electrocardiogram taken on March 2 was likewise normal.

CASE 2.—A white Amercan soldier, aged 27, was admitted to an army station hospital in Panama on Oct. 18, 1943, with the chief complaint of a swollen right eye of seven days' duration. He had been on duty in Panama for the past twenty-four months, and his only previous illness had been an attack of malarial fever in May 1942. He dated the onset of his present illness to one week prior to his admission to the hospital, when he began to notice progressive painless swelling of the right eye. Forty-eight hours before his admission, he experienced mild generalized malaise and fever but no chills, sweats or headache. The eye, though extremely swollen at that time, was not painful, nor was there an excessive secretion of tears or any discharge. There were no symptoms referable to the cardiac, respiratory, gastro-

intestinal or genitourinary systems. Local medication applied at his battalion aid station produced no beneficial effects on the ocular edema, and with the development of fever and malaise he was sent to the hospital. On further subsequent questioning, the additional history was elicited from the patient that in the vicinity of the hutment in which he had been quartered there were many "cone-nosed bugs." He had observed these insects on many occasions attempting to gain entrance into the screened enclosure at night, and on several occasions he had crushed these insects when they were clinging to his clothing and had noticed that they gave evidence of previous blood meals. He also remembered that between two and three weeks previously he and several of his companions had captured a sloth on which "cone-nosed" insects were feeding. He had no recollection of any insect bites.

Examination shortly after his admission to the hospital revealed an alert, cooperative, well developed and well nourished man who did not appear acutely ill. The temperature was 101 F. and the pulse rate 100 per minute. The right eye was almost completely closed by edema of both the upper and the lower lids (fig. 3). The edema extended outward to involve the soft tissues of the right malar eminence. The overlying skin revealed a pinkish discoloration. The area was not painful and did not pit on pressure. Though firm in consistency, the tissues were elastic and without evidence of subcutaneous infiltration. The conjunctival surfaces were hyperemic, with scanty secretion. The right preauricular lymph node was enlarged, firm and slightly tender. Scattered over the anterior thoracic wall, shoulders, upper arms, forearms, abdomen and back were discrete, circumscribed macular blanching erythematous plaques, varying in size roughly from that of a 25 cent coin to that of a silver dollar. Some of the lesions did not blanch completely on pressure and felt infiltrated but were not elevated. A few showed confluence, but the majority were distinct and separate. These lesions were asymptomatic, and the patient had not noticed them. At no time were they painful or pruritic. The thyroid gland was not found to be enlarged on initial or subsequent examinations. The lungs were observed to be clear on percussion and auscultation. Percussion revealed no cardiac enlargement, and no murmurs or arrhythmias were noted. The blood pressure was 130 mm. of mercury systolic and 68 mm. diastolic. The remainder of the physical examination revealed nothing abnormal.

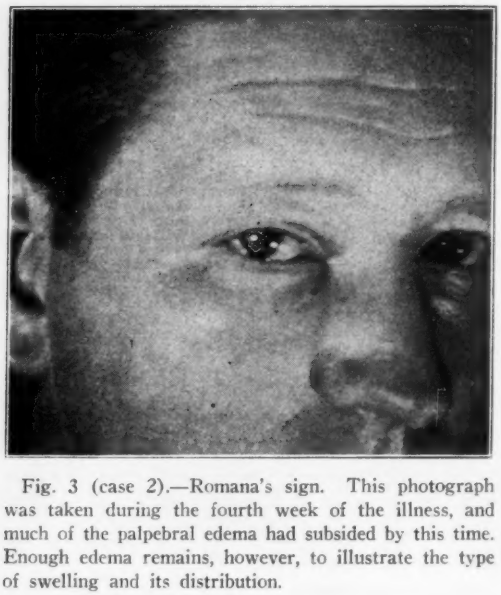

Fig. 3 (case 2).—Romana's sign. This photograph was taken during the fourth week of the illness, and much of the palpebral edema had subsided by this time. Enough edema remains, however, to illustrate the type of swelling and its distribution.

Course in Hospital.—On the basis of the history and physical observations, a clinical diagnosis of Chagas' disease was made. It was not until the twenty-sixth day of his illness, however, that the clinical diagnosis was confirmed by laboratory evidence. On that day his complement fixation reaction was found to be strongly positive. One tested previously during the first week of his illness had been reported as negative. On the thirty-first day of his illness additional laboratory proof was evidenced when T. cruzi was demonstrated in the blood and tissues of 1 of the guinea pigs that had been inoculated with the patient's blood during the first week of his illness. Repeated attempts during this time to demonstrate the parasite in thick and thin blood films were unsuccessful.

During the first two weeks of his illness the patient had a daily temperature varying between 99 and 103 F. and showed signs of increasing debility. Because of the apparently beneficial results from antimony observed in case 1, treatment with fuadin was started on the eleventh day of his illness, it being decided that his clinical course was such that a further wait for laboratory confirmation would not be justified. He received the drug by intramuscular injection at spaced intervals during the next eight weeks; a total of 83 cc. of the drug was administered in two courses, with a two week interval during which none was administered. There was a gradual fall in temperature during the first two weeks of drug therapy, when the temperature varied between 99 and 101.5 F. Thereafter he had a slight daily elevation of temperature until December 18. During this period, the cutaneous rash faded and had completely disappeared by the seventeenth day in the hospital. No desquamation, scarring or recurrence of the rash was observed. The edema of the eye gradually subsided during the first seven weeks, although a residual discoloration of the lids persisted for several weeks afterward. The enlarged preauricular lymph node decreased in size from the thirty-second to the sixtieth day, when it could no longer be palpated. In addition to the previously described enlargement of a lymph node, during the second week of his illness a shotty lymphadenopathy of the posterior chain of cervical lymph nodes developed. These persisted until the fortieth day of his illness. Testicular pain was complained of during the third and fourth week of his illness. No swelling of either testis or epididymis was observed.

Early in the course of his illness, despite various apparent improvements, including the lowering of his temperature, decrease in the ocular edema and clearing of his cutaneous eruption, it became apparent that the patient was suffering cardiac damage. During the third week of his illness the slightest exertion resulted in prolonged tachycardia, and during the fourth week of his illness tachycardia at absolute rest became apparent. A soft apical systolic murmur became manifest at this time, along with frequent runs of ventricular extrasystoles and a diastolic gallop rhythm. The last was associated with electrocardiographic evidence of a prolonged PR interval. The rhythm changed frequently, and dropped beats were evident. The heart sounds were of poor tonal quality, suggesting a flabby myocardium. By percussion the left cardiac border was interpreted as being increased, as compared with the size determined

on his admission to the hospital. Confirmatory roentgenographic evidence of left ventricular enlargement was also obtained at this time. Additional evidence of myocardial damage was found in the changes observed in the serial electrocardiograms that were taken. During the early stage of the disease these revealed pronounced inversion of the T waves consistent with serious myocardial damage.

Although pericardial effusion has been reported in cases of Chagas' disease,[25] it is not common, and it is our opinion that the electrocardiographic and roentgenographic findings represented changes due to diffuse myocardial damage with cardiac dilatation rather than incident to an undetected pericardial effusion. With return of the cardiac silhouette to normal, the T waves became upright, but the electrocardiographic tracings continued to show evidence of a severe conduction disturbance between the auricle and ventricles. Thus it is evident that, in addition to diffuse myocarditis, focal lesions in the conducting system also occurred.

From the fourth to the eighteenth week of the patient's illness it was daily noted that his pulse and cardiac rate and rhythm were subject to wide and frequent variations. An explanation for this changing rate and rhythm was found in the electrocardiographic studies. These showed that the irregularities of rate and rhythm were chiefly due to ventricular extrasystoles and second degree auriculoventricular block. Occasional beats showed delayed intraventricular conduction.

Rapid changes in the degree of block were noted from day to day and on several occasions from hour to hour. No reasonable explanation for these could be determined, and they did not seem to represent or coincide with any other physical findings or to evidence any tendency toward regression or progression of the disease.

During this period, when it was apparent that progressive and severe cardiac damage was occurring, no subjective symptoms except palpitation were ever experienced by the patient. At no time were there any signs or symptoms of circulatory or cardiac failure. The blood pressure remained in the vicinity of the original determination throughout his entire stay in the hospital.

The myocardial damage, though severe, was not entirely irreversible, however, as was shown by improvement in his electrocardiographic tracings during the seventh week of his illness and by a return of the size of his heart to normal during the ninth week of his illness. The pathologic changes which occurred in the auriculoventricular conducting pathway are apparently of a permanent nature, since little or no improvement of the heart block was noted during the period of over five months that he was under observation.

Laboratory Studies.—Repeated blood counts revealed essentially normal values for hemoglobin and red blood cells. On November 5, the white blood cell count rose to 13,300, with a definite increase in the lymphocytes (table 2). For several days prior to this, during examinations of blood films for trypanosomes, atypical lymphocytes of the type seen in infectious mononucleosis were observed. The heterophile antibody reaction was positive at this time. Later, this reaction became negative. A significant degree of lymphocytosis was present throughout most of the patient's stay in the hospital, a period of over five months.

These hematologic observations are presented in tabular form (table 2) and show a similarity to those recorded in the first case.

Repeated studies of thick blood smears for trypanosomes and malarial parasites revealed no parasites. On October 23 and again on October 24, 5 cc. of whole blood was inoculated into the peritoneal cavity of each of 2 guinea pigs. One of the animals died on November 16, and autopsy revealed groups of multiplying leishmanial forms of T. cruzi in the tissue and trypanosomal forms in the blood. The complement fixation reaction (Johnson and Kelser modifications of the Guerreiro-Machado test) was negative on October 23, strongly positive on November 12 and 23, positive but with falling titer on December 18 and 29 and January 9, 1944 and negative on January 19, February 4 and February 29. (These tests were performed for us at the Gorgas Memorial Laboratory by Dr. Johnson.)

The Kahn reaction of the blood serum was negative on two occasions.

The total serum protein was 6.9 and 7.5 Gm. per hundred cubic centimeters, with an albumin-globulin ratio of 1.3.

Repeated cultures of the blood showed no growth.

The heterophile antibody reaction occurred in a titer of 1:896 on November 25 and in a titer of 1:448 on December 1. It was negative on December 14.

Repeated examinations showed the urine to be normal.

Repeated roentgenographic examination of the chest revealed no consolidation, infiltration or pleural effusion. The cardiac measurements are shown in table 3.

Serial electrocardiograms were taken during the course of the patient's illness. Some of these were selected for mention in order to demonstrate the more important changes.

TABLE 2.—*Results of Hematologic Examinations (Case 2)*

Date	Red Blood Cells	Hemoglobin	White Blood Cells	Polymorphonuclear Leukocytes	Lymphocytes	Eosinophils	Mononuclear Leukocytes	Blood Sedimentation Rate, Mm.	Comment
October 19	.....	..	4,100	66	34	..	..	..	
October 22	.....	..	4,650	58	34	1	7	..	
October 24	.....	..	4,150	49	51	..	..	21	
November 2	4,300,000	85	7,200	48	52	..	..	..	
November 5	4,600,000	98	13,300	18	81	1	..	..	
November 7	.....	..	8,300	34	66	..	..	..	
November 11	4,900,000	98	6,600	32	68	..	..	..	Presence of atypical lymphocytes
November 15	4,150,000	90	6,900	47	48	5	..	20	
November 22	.....	..	.....	..	..	..	..	15	
December 5	.....	..	.....	..	..	..	..	10	
December 11	.....	..	6,050	37	57	6	..	..	
January 4	4,060,000	90	8,100	46	52	2	..	14	
January 20	4,700,000	95	7,950	40	52	7	1	13	
February 5	.....	..	7,000	41	53	5	1	4	
March 1	5,050,000	95	7,500	50	40	1	..	5	

25. Lundeberg, K. R.: A Fatal Case of Chagas Disease Occurring in a Man 77 Years of Age, Am. J. Trop. Med. **18**:185, 1938.

The first tracing, taken on October 24, revealed a sinus mechanism, a rate of 89 per minute and an auriculoventricular conduction time of 0.16 second. The T waves were upright in leads I and II and diphasic in lead III. The precordial lead was normal. The next electrocardiogram, taken on November 4, revealed a rate of 80 per minute, flattened P and T waves and a significant decrease in the amplitude of the QRS complexes in all leads. Thereafter, serial electrocardiograms, taken on November 7, 9, 10 and 19, revealed progressive inversion of the T waves in the standard and precordial leads without any deviation of the ST segments. On November 19, the rate was 83 per minute and the auriculoventricular conduction time 0.17 second, and the T waves were more deeply inverted and coronary in appearance. The second beat in lead I of this record revealed a transient intraventricular block of the peculiar form in which the prolongation of the QRS complex is associated with a reduction of the PR interval. In this beat, the PR interval was reduced from 0.17 to 0.10 second and the QRS complex prolonged from 0.06 to 0.12 second. In the electrocardiogram taken November 22, the PR interval was recorded as being prolonged to 0.20 second, in contrast to the previous 0.17 second. This record also revealed frequent ventricular premature systoles. The tracing on November 26 revealed a normal auriculoventricular conduction time of 0.17 second, upward bowing of the ST segments and further inversion of the T waves. On December 4, the rate was 93 per minute, the PR interval 0.18 second and the T waves less deeply inverted. On December 7, the tracing revealed a prolonged auriculoventricular conduction time of 0.22 second. This had receded to 0.18 second on December 10. On December 14, the rate was 107 per minute and the PR interval 0.28 second. From December 4 to January 1, the T waves became less deeply inverted in spite of the evidence of persistent auriculoventricular heart block. The tracing on Jan. 1, 1944 revealed a first degree auriculoventricular block, with a PR interval of 0.28 second and upright T waves in leads I, II and IV. On January 23, second degree auriculoventricular block with Wenckebach's period was present. From then to the end of our period of observation, the rhythm varied between first and second degree auriculoventricular block, with transient intraventricular conduction defect.

TABLE 3.—*Cardiac Measurements (Case 2)*

Date	Transverse Cardiac Diameter, Cm.	Transverse Thoracic Diameter, Cm.
October 19	12.3	31.2
November 12	14.5	31 1
November 19	14.2	30.6
December 18	12.7	31.2
December 30	12.9	31.2

COMMENT

Certain features of the disease in these 2 cases should be emphasized, since they differ in some ways from those of previously reported cases.

In spite of the repeated previous observations in this area by Clark, Johnson and De Rivas on the benign character of the disease, particularly among adults, South American trypanosomiasis in Panama can constitute a serious illness for adults. To our knowledge, these are the first and only 2 instances in which this disease has been contracted by other than native-born persons in this area. Perhaps this fact explains why the disease took a more severe form in these 2 men than had been previously observed in adults.

The degree of symptomatic illness apparently has little prognostic value. The first patient appeared as severely ill as the second but completely recovered, while in the second severe cardiac damage developed. There was nothing in the past histories, the physical fitness of the 2 soldiers or in the degree of parasitemia exhibited which can explain this difference in the clinical courses observed. As in other disease agents, pathogenicity undoubtedly varies with different strains.

Articular symptoms and signs have not to our knowledge been previously described as a part of the clinical picture of Chagas' disease, but, as observed in case 1, these can be prominent manifestations of the illness.

Mazza previously emphasized [9] that the finding of a sustained increase in the lymphocyte count during the latter part of the acute stage of Chagas' disease appears to be of some diagnostic value. In both of our patients lymphocytosis occurred during the fourth and fifth week of the illness and continued during the next two months. In the second patient this response was more pronounced than in the first, and examination of his blood film revealed many young and abnormal lymphocytes. These, combined with the finding of a strongly positive heterophile antibody reaction of the serum, raised the question as to whether the second patient might not have also had infectious mononucleosis. There were, however, no other symptoms of this disease present.

Only repeated observations on other patients with Chagas' disease can provide an acceptable answer to the question.

It is interesting to note also that it was during the time that the complement fixation reaction began to fall in titer that the heterophile antibody reaction became negative.

An unusual degree of eosinophilia was not observed in either patient.

Although most of the published clinical reports of the cardiac damage observed in Chagas' disease in adults deal with the so-called chronic cases, it is evident from the observations made in case 2 that such damage may also occur during the acute stage of the disease in adults. Severe myocarditis during the acute stage is not necessarily limited to children, as some investigators have thought. Cardiac damage, though it may be severe, does not necessarily always produce a sudden or immediate death. Some degree of healing can occur. After five months of obser-

vation, we are led to believe that the cardiac lesions of the patient in case 2 have healed considerably and to deduce further from all clinical signs and symptoms and from the results of our laboratory studies that further progress of the disease seems unlikely. The damage incurred by the conducting pathways is apparently permanent, however, and that some degree of permanent cardiac incapacity will result is the most probable prognosis at this time.

In many respects the disease resembles acute rheumatic fever, from which it must be differentiated. Recent reports and our own experience in the past two years indicate that acute rheumatic fever is not an infrequent disease among soldiers in the tropics. The high fever, articular pain, polymorphous and urticarial cutaneous lesions, pericarditis, electrocardiographic evidence of disturbance in conduction between the auricles and ventricles, abnormal T waves and roentgenographic evidence of cardiac enlargement are common to both diseases.

Our experience with fuadin in the treatment of this disease has been limited to these 2 instances. At the present time, there is no specific treatment for Chagas's disease. Since the antimony compounds are of definite value in the treatment of leishmanial forms of similar parasites and since this is the form of the trypanosome which actually causes the cellular and tissue damage, we felt justified in using this form of antimony in the treatment of our 2 patients. From the available reports, Bayer 7602 (Ac)[26] does not appear to offer much more in the way of therapeutic success and is apparently more toxic than fuadin.

We do not claim any remarkable therapeutic results in our 2 cases, and investigators with more experience do not think antimony preparations of much value. Clinically, its administration appeared to coincide with or cause the temperature to subside, to alleviate the articular symptoms in our first case and to bring about subjective improvement in both. Another observation suggesting antimony to have some merit is that the complement fixation reaction became negative in the second patient after its administration. If this test is at all analogous to other complement fixation tests as an indication of the progress and prognosis of a disease, this change is indicative that the infection has been eradicated although its scars are still present. Johnson's experience with this complement fixation test in Panama has been that the reaction remains positive in untreated patients for several years after the initial discovery of the parasites in the blood stream though no clinical evidence of the disease exists, thus suggesting that the infection remains present though in a latent stage.[1a]

26. Bayer 7602 (Ac) is a substance which consists of two 2-methyl-4-aminoquinoline groups joined by a diallyl malonyl group in position 6.

SUMMARY AND CONCLUSIONS

The diagnosis of acute South American trypanosomiasis has been made in 2 additional cases in Panama, thus making a total of 21 cases of this disease which have been clinically studied in this area since 1931 and a grand total of 58 cases in which the diagnosis has been made. The disease occurred in young adult white soldiers stationed in this area. In contradistinction to the cases previously reported from this country observed in adults, the infection gave rise to a serious illness in both these soldiers and was more akin to the acute clinical picture as it has been described in other areas. These are the first 2 instances in which the infection has been diagnosed in other than native-born inhabitants in this country.

Serial electrocardiograms were made, and the cardiac manifestations of the disease were studied in 1 patient with acute Chagas' disease.

It is emphasized that articular symptoms and signs may occur as a manifestation of this disease and that these and many of the other features of acute Chagas' disease may closely simulate the disease pattern of rheumatic fever.

Lymphocytosis, as Mazza has previously pointed out, appears to be a laboratory finding of clinical significance in Chagas' disease.

In treatment of these 2 patients, antimony appears to have been of therapeutic value.

SICKLE CELL ANEMIA IN WHITE PATIENTS WITH ULCERS OF THE ANKLES

REPORT OF TWO CASES

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DES MOINES, IOWA PARKERSBURG, W. VA. DES MOINES, IOWA

Sickle cell anemia, since it was described by Herrick in 1910,[1] has been known almost exclusively as a disease of the Negro race. However, after the report of Cooley and Lee in 1929, numerous instances of the disease have been reported in patients mostly of Greek, Sicilian and Italian extraction, thought to be without Negro ancestors.[2] The white patients mentioned in these reported cases have presented evidence of sickle cell anemia, including sickling, greenish yellow scleras, hepatomegaly, splenomegaly, pains in the joints, arms or legs and occasionally abdominal crises. All available case histories of the disease in the white race have failed to mention or have noted the absence of ulcerations or scars of the ankles or legs. It is our purpose to report on 2 patients from one family, 1 male and 1 female, with ulcers of the ankles and limitation of motion about the ankle joints.

The family history revealed that the grandmother on the paternal side was the first relative to have pallor and ulcers of the ankles. The parents of this ancestor were known to be of the white race, without negroid features, and died at the age of 84 and 86. The father, aged 47, and the uncle, aged 45, were pale and had had recurrent ulcerations of the ankles since childhood. The 2 patients presented evidence of sickle cell anemia; another brother had delayed sickling, and a third brother was normal (fig. 1).

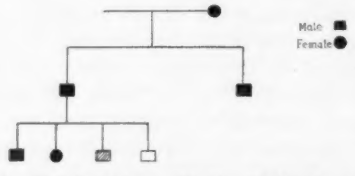

Fig. 1.—Family tree. Shading indicates members with ulcers of the ankles and pallor; slanting lines indicate member with sickling trait only, and white space indicates normal member.

COMMENT

Sicklemia, a latent form of sickle cell anemia, is inherited as a mendelian dominant characteristic.[3] The hemoglobin content and erythrocyte counts are normal or nearly normal. Examination of a preparation of fresh blood from patients with sicklemia sealed from three to twenty-four hours reveals the presence of sickle cells. Bauer and Fisher [4] stated that the usual

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1. Herrick, J. B.: Peculiar Elongated and Sickle-Shaped Red Blood Corpuscles in a Case of Severe Anemia, Arch. Int. Med. **6**:517-521 (Nov.) 1910.

2. Cooley, T. B., and Lee, P.: Sickle Cell Anemia in a Greek Family, Am. J. Dis. Child. **38**:103-106 (July) 1929. Cooke, J. V., and Mack, J. K.: Sickle Cell Anemia in a White American Family, J. Pediat. **5**:601-605 (Nov.) 1934. Clarke, F.: Sickle Cell Anemia in the White Race with Report of Two Cases, Nebraska M. J. **18**:376-379 (Oct.) 1933. Greenwald, L.; Spielholz, J. B., and Litwins, J.: Sickling Trait in a White Adult Associated with Hemolytic Anemia, Endocarditis and Malignancy, Am. J. M. Sc. **206**:158-168 (Aug.) 1943. Greenwald, L., and Burrett, J. B.: Sickle Cell Anemia in a White Family, ibid. **199**:768-774 (June) 1940. Haden, R. L., and Evans, F. D.: Sickle Cell Anemia in the White Race, Arch. Int. Med. **60**:133-142 (July) 1937. Rosenfeld, S., and Pincus, J. B.: The Occurrence of Sicklemia in the White Race, Am. J. M. Sc. **184**:674-682 (Nov.) 1932. Weiner, S. B.: Sickle Cell Anemia in an Italian Child, J. Mt. Sinai Hosp. **4**:88-91 (July-Aug.) 1937. Johnson, F. B., and Townsend, E. W.: Sickle Cell Anemia, South. Med. & Surg. **99**:377-381 (Aug.) 1937. Sights, W. P., and Simon, S. D.: Marked Erythrocytic Sickling in a White Adult Associated with Anemia, Syphilis and Malaria, J. Med. **12**:177-178 (June) 1931. Vance, B. M., and Fisher, R. C.: Sickle Cell Disease, Arch. Path. **32**:378-386 (Sept.) 1941. Wade, L. J., and Stevenson, L. D.: Necrosis of the Bone Marrow with Fat Embolism in Sickle Cell Anemia, Am. J. Path. **17**:47-54 (Jan.) 1941. Morrison, M.; Samwick, A. A., and Landsberg, E.: Sickle Cell Anemia in the White Race, Am. J. Dis. Child. **64**:881-887 (Nov.) 1942. Stewart, W. B.: Sickle Cell Anemia: Report of a Case with Splenectomy, ibid. **34**:72-80 (July) 1927. Ogden, M. A.: Sickle Cell Anemia in the White Race with Report of Cases in Two Families, Arch. Int. Med. **71**:164-182 (Feb.) 1943.

3. Steinberg, B.: Sickle Cell Anemia, Arch. Path. **9**:876-897 (April) 1930. Sydenstricker, V. P.: Sickle Cell Anemia, M. Clin. North America **12**:1451-1457 (March) 1929. Dreyfoos, M.: Sickle Cell Anemia, Arch. Pediat. **43**:436-447 (July) 1926.

4. Bauer, J., and Fisher, L. J.: Sickle Cell Disease, Arch. Surg. **47**:553-563 (Dec.) 1943.

hazards of sickle cell anemia may never appear in such patients during an otherwise normal lifetime.

However, patients with true sickle cell anemia, children and adults, exhibit signs, symptoms and laboratory evidences of mild to profound anemia. Exacerbations and remissions occur at irregular intervals. Pallor, dyspnea, fatigue and palpitation frequently exist over a long period. A greenish yellow color of the scleras has been noted and occasionally icterus. Pains in the arms and legs may simulate those of rheumatic fever. Physical examination reveals pallor, malnutrition, evidences of hemolysis, with yellow scleras and at times enlargement of the liver and spleen, lymphadenopathy and an apical systolic murmur. Ulcers on the legs or ankles, unilateral or bilateral, have appeared in Negro patients spontaneously or after mild traumas. Healing is prolonged and followed by scarring.

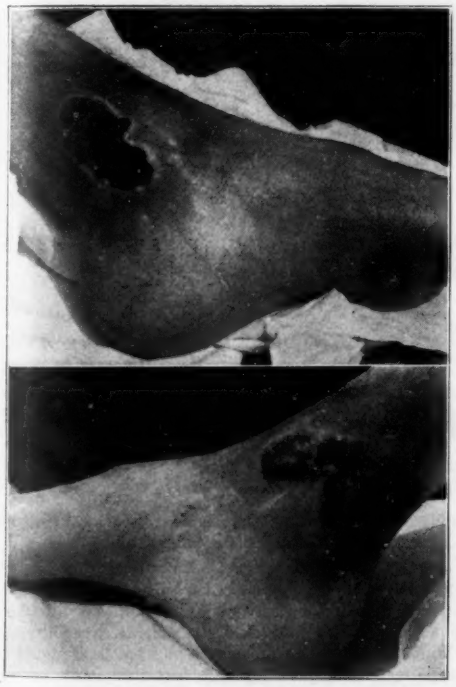

Fig. 2 (case 1).—Chronic ulcers of both ankles.

Roentgenograms, according to Diggs, Pulliam and King [5] have in most cases been normal. However, they and others have described changes in the thickness of the skull, changes in the outer and inner tables and "hair on end" phenomena. Osteoporosis and osteosclerosis in bones other than those of the skull are less evident.

Bauer and Fisher [4] and Canby, Carpenter and Ellmore [6] called attention to the importance to the surgeon of making a diagnosis in the absence of sickle cells in the stained blood film, since the risk to the surgical patient is increased by

Fig. 3 (case 1).—Closeup of chronic ulcer of the ankle showing pigmentation and cicatrization.

sickle cell anemia. Tests for delayed sickling reactions should be done in the presence of atypical medical and surgical conditions. The disease has been noted as a cause of cor pulmonale,[7] and occasionally in association with cholecystitis.[8] It has been mistaken for rheumatic fever, microcytic anemia, pernicious anemia, acute appendicitis and cholecystitis. Infectious mononucleosis has been reported in 1 patient.[9]

The blood picture varies from a normal or nearly normal hemoglobin content and erythrocyte count in latent sickling to a profound anemia during relapse. Sickle cells are often not found in the former stage until a wet preparation is

5. Diggs, L. W.; Pulliam, H. N., and King, J. C.: The Bone Changes in Sickle Cell Anemia, South. M. J. **30**:249-259 (March) 1937.

6. Canby, C. B.; Carpenter, G., and Ellmore, L. F.: Drepanocytosis (Sicklemia) and an Apparently Acute Surgical Condition of the Abdomen, Arch. Surg. **48**: 123-125 (Feb.) 1944.

7. Yater, W. M., and Hansmann, G. H.: Sickle Cell Anemia: A New Cause of Cor Pulmonale, Am. J. M. Sc. **191**:474-484 (April) 1936.

8. Schaefer, B. F.: Sickle Cell Anemia and Cholelithiasis, M. Ann. District of Columbia **11**:392-396 (Oct.) 1942. Weens, H. S.: Cholelithiasis in Sickle Cell Anemia, Ann. Int. Med. **22**:182-191 (Feb.) 1945.

9. Ray, E. S., and Cecil, R. C.: Infectious Mononucleosis in the Negro: Report of Three Cases with One Complicated by Sickle Cell Anemia, South. M. J. **37**: 543-545 (Oct.) 1944.

sealed and left for as long as twenty-four hours, when more than 40 per cent are frequently found.

Polychromatophils, erythroblasts, microcytes, macrocytes, reticulocytes and sickling of more than 4 per cent of the erythrocytes, with even more affected by a delayed sickling reaction, characterize the severe type of anemia. Target cells, erythrocytes resembling a target or bull's eye, have been described in sickle cell and other anemias.[10] The mean corpuscular volume may be that characteristic of either a microcytic or a macroscopic anemia. Leukocyte counts are usually elevated, with an increase in the lymphocytes and the occasional presence of 1 to 3 per cent eosinophils.

Treatment is known to have little influence on the sickling trait or the anemia. Blood transfusions may be necessary during a relapse. Rest is indicated for patients with ulcers of the ankles.

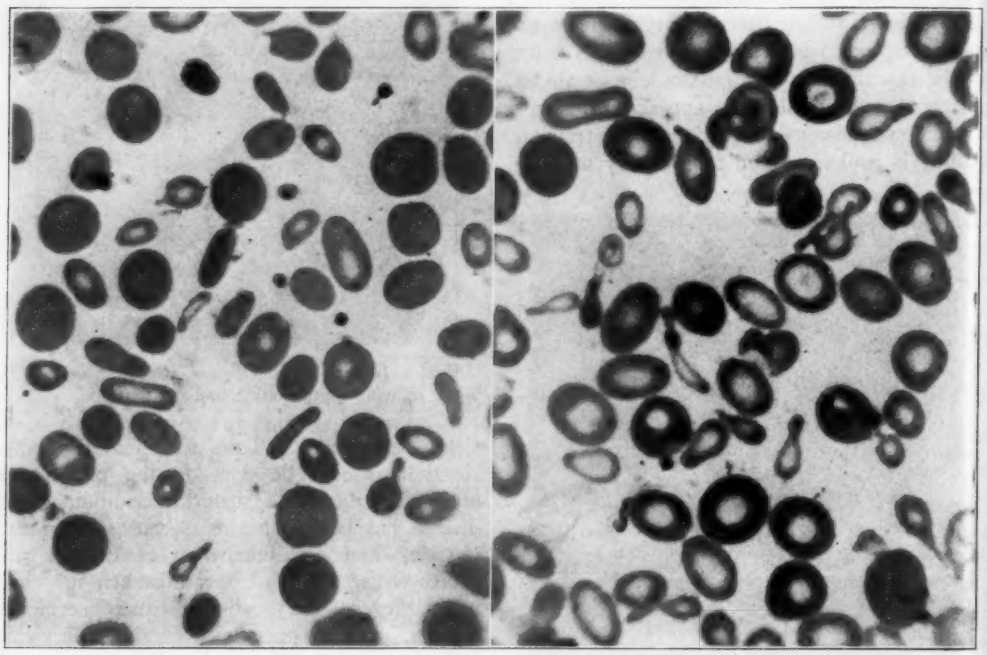

Fig. 4 (case 1).—Photomicrographs of stained blood smear (not sealed).

REPORT OF CASES

CASE 1.—A 20 year old white youth was admitted to the hospital in August 1940, complaining of ulcers on both ankles. When he was 13, after an attack of dermatitis venenata (ivy poisoning), ulcers appeared on both ankles and have persisted until his admission. These were painful only on walking, but he had been unable to work or attend school for five years. Dyspnea and palpitation on exertion, as well as pallor, fatigue and malnutrition, were known to have been present for seven years. Discoloration of the scleras had been noted, but for an unknown length of time. Moderately severe muscular pains in the arms and legs were aggravated by fatigue. There had been no abdominal crises and no known febrile attacks.

The family history revealed that the paternal grandmother, who first had ulcers of the ankles and pallor, died at 58 years of age. The father, aged 47, and the uncle, aged 45, had pallor and scarring and fixation of both ankle joints. One sister, aged 14, was extremely pale and had a small ulcer on the inner aspect of the right ankle. Two brothers had neither pallor nor ulcers (one had delayed sickling). The mother was normal. The parents of the grandmother, the first member of the family with the disease, were known by a local historian to have been normal and of the white race.

Physical examination revealed a pallor of the lips and conjunctivas in a malnourished white youth, who seemed younger than his stated age. The skin was discolored by a pale yellow tint, and the scleras were greenish yellow. The tongue was smooth and red laterally. Both tonsils were enlarged, and there was a moderate cervical lymphadenopathy. The pulmonary fields were normal to inspection, palpation, percussion and auscultation. A systolic murmur was heard at the apex and was transmitted over the entire precordium. There was a moderate widening of the left border of cardiac dulness. The cardiohepatic angle was normal to percussion. The heart rate and rhythm were normal. A mass with a palpable notch was felt in the left upper quadrant of the abdomen 3 fingerbreadths below the costal margin. The liver was palpated 3 fingerbreadths below the right costal margin. There was no spasticity of the abdominal muscles or tenderness over any point. The knee jerks were equal on the two sides and were slightly dimin-

10. Dameshek, W.: Familial Mediterranean Target-Oval Cell Syndromes, Am. J. M. Sc. **205**:643-660 (May) 1943.

ished. Sensations of heat, cold, vibration and deep tendon pain were retained. The Babinski reflex was elicited. Two large ulcers were present on the inner aspects of both ankles (figs. 2 and 3).

Laboratory observations revealed: hemoglobin content, 55 per cent (Sahli); red blood cells, 3.67; color index, 0.67; mean corpuscular volume, 58; platelet count, 225,040, and white blood cells, 17,850, with band forms 38 per cent, segmented forms 52 per cent and lymphocytes 10 per cent. One per cent of erythrocytes showed basophilic stippling, and 15 per cent showed sickling, increasing to 40 per cent with delayed sickling. The erythrocytes varied greatly in size and shape, including macrocytes, microcytes and many polychromatophilic cells. Most erythrocytes were pale. A few nucleated red cells were present. The corrected sedimentation rate was 9 mm. in one hour; the bleeding time was three minutes. The Wassermann and Kahn reactions were negative. The urinalysis was normal, except for giving a strongly positive reaction for urobilin. Roentgenograms showed that there was no "hair on end" phenomena in the skull and that both ankle joints were normal.

Case 2.—The 14 year old sister of the first patient was seen as an outpatient with a small ulcer on the right ankle, which had existed for approximately three weeks. Dyspnea on exertion, fatigue, pallor and malnutrition had been present since early childhood. There had been no abdominal pain or febrile attacks.

Physical examination revealed a slender, pale young white girl. Several small cervical lymph nodes were palpable. Examination showed the chest to be normal. A soft systolic murmur was heard at the apex and was transmitted over the precordium. The abdomen was normal. A small ulcer, less than 1 inch (2.5 cm.) in diameter, was present on the right ankle.

Laboratory data were as follows: hemoglobin content, 60 per cent (Sahli); red blood cells, 3.77; color index, 0.75, and white blood cells, 7.4, with band forms, 16 per cent; segmented forms, 62 per cent; lymphocytes, 20 per cent and monocytes, 2 per cent. Erythrocytes varied in size and shape, including macrocytes and microcytes, and 18 per cent showed sickling. Delayed sickling increased the sickle cells to 30 per cent. The mean corpuscular volume was 75 cubic microns; the platelet count was 266,760. Hemolysis of erythrocytes began at 0.37 per cent and was complete at 0.24 per cent. The Wassermann and Kahn reactions were negative. The urine was normal. (The test for urobilin was not done.)

CLINICAL SYNDROME IN PATIENTS WITH PULMONARY EMBOLISM

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It has been known for some time, but not generally appreciated, that pulmonary embolism may simulate many other conditions. Over thirty years ago attention was called to the fact that pulmonary embolism might be confused with pleurisy,[1] angina pectoris [2] and lobar pneumonia.[3] Since then the similarity between pulmonary embolism and other commonly accepted syndromes has been casually referred to in statistical studies or in individual case reports.[4] White [5] has pointed out that unexplained fainting, prostration, dyspnea, tachycardia, fever or jaundice should suggest the diagnosis of pulmonary embolism.

Failure to recognize the many clinical manifestations of pulmonary embolism may lead to erroneous diagnosis and prevent application of proper therapeutic and prophylactic procedures. In order to gain a more comprehensive view of the total clinical picture of pulmonary embolism than is now available, all cases at the Beth Israel Hospital, Boston, from 1929 to 1942, inclusive, with the diagnosis of pulmonary embolism were reviewed. Only those cases were selected in which the diagnosis was reasonably certain; the demonstration of a source of embolism was considered desirable but not essential. Of 500 cases reviewed, 108, including 32 cases studied at autopsy, were selected for study. There were 76 cases in which recovery occurred or postmortem examination was not performed. In 61 of these cases roentgenologic evidence of pulmonary infarction and/or electrocardiographic changes consistent with acute cor pulmonale [6] were present, and in 50 of these there was a definite source of embolism. In 9 cases, the clinical picture was consistent with pulmonary embolism and the source of embolism was demonstrable. Thus of the total of 108 cases, 102, besides showing a consistent clinical picture, satisfied any one or a combination of the following criteria: evidence at autopsy of pulmonary embolism, electrocardiographic pattern of acute cor pulmonale, roentgenographic evidence of pulmonary infarction or demonstration of the probable source of embolism. Of the remaining 6 cases, there were 4 cases of sudden postoperative death in patients under the age of 40 without any antecedent history of hypertension or cardiovascular disease, and in only 2 cases diagnosis was made entirely on the basis of the clinical picture. Cases of mitral stenosis and congestive failure, subacute bacterial endocarditis with embolic phenomena and sudden postoperative death in elderly patients without any other evi-

1. Miller, G. B.: The Significance of Postoperative Pleurisy: Its Relation to Pulmonary Embolism, Am. Med. **4**:173, 1902.

2. Von Neusser, E.: Angina Pectoris, New York, E. B. Treat & Company, 1909.

3. Conner, L. A.: A Pulmonary Attack Simulating Primary Lobar Pneumonia, Caused by Pulmonary Embolism and Infarction from a Latent Venous Thrombosis, Arch. Int. Med. **13**:349 (March) 1914.

4. (*a*) Hamburger, W. W., and Saphir, O.: Pulmonary Embolism Complicating and Simulating Coronary Thrombosis, M. Clin. North America **16**:383, 1932. Averbuck, S. E.: The Differentiation of Acute Coronary Thrombosis from Pulmonary Embolization, Am. J. M. Sc. **187**:391, 1934. Scherf, D., and Schönbrunner, E.: Ueber Herzebefunde bei Lungenembolien, Ztschr. f. klin. Med. **128**:455, 1935. Gorham, L. W.: The Differential Diagnosis of Acute Occlusion of the Coronary and Pulmonary Arteries, Albany M. Ann. **55**:91, 1936. Haggard, J. B., and Palmer, R. S.: A Case of Pulmonary Embolism Simulating Coronary Thrombosis in a Young Man Aged Thirty-Three Years, Am. Heart J. **12**:748, 1936. Pilcher, R.: Slowly Fatal Pulmonary Embolism, Lancet **2**:942, 1938. Johnson, A. S.: The Antemortem Recognition of Pulmonary Embolism, New England J. Med. **222**:793, 1940. Freston, J. M.: Pulmonary Embolism-Diagnosis, New York State J. Med. **41**:1843, 1941. Currens, J., and Barnes, A. R.: The Heart in Pulmonary Embolism, Arch. Int. Med. **71**:325 (March) 1943. Murnaghan, D.; McGinn, S., and White, P. D.: Pulmonary Embolism With and Without Acute Cor Pulmonale, with Especial Reference to the Electrocardiogram, Am. Heart J. **25**:573, 1943. (*b*) Homans, J.: Pulmonary Embolism Due to Quiet Venous Thromboses and Simulating Cardiac and Pulmonary Disease, New England J. Med. **229**:309, 1943.

5. White, P. D.: Pulmonary Embolism and Heart Disease: A Review of Twenty Years of Personal Experience, Am. J. M. Sc. **200**:577, 1940.

6. McGinn, S., and White, P. D.: Acute Cor Pulmonale Resulting from Pulmonary Embolism: Its Clinical Recognition, J. A. M. A. **104**:1473 (April 27) 1935. Barnes, A. R.: Diagnostic Electrocardiographic Changes Observed Following Acute Pulmonary Embolism, Proc. Staff Meet., Mayo Clin. **11**:11, 1936.

dence pointing to pulmonary embolism were not included. Thus, the selection of cases was rigid, and, while some cases of pulmonary embolism were undoubtedly excluded, the diagnosis in all probability was correct in the 108 cases chosen for study.

ANALYSIS OF DATA

The individual symptoms and signs and laboratory data observed in the 108 cases were tabulated (tables 1 and 2). Since the clinical manifestations of pulmonary embolism tend to appear in recurring attacks or episodes, many of the symptoms and signs were present more than once in some of the patients. Each appearance of a symptom or sign or of a combination of them is referred to as a clinical episode. Certain individual symptoms and signs or combinations of them in a given patient simulated diseases or syndromes other than pulmonary embolism (table 3).

TABLE 1.—*Signs and Symptoms Found in Association with Pulmonary Embolism*

Signs and Symptoms	Number of Cases (Total 108)	Number of Clinical Episodes (Total 162)
Pain:		
Pleuritic	54	66
Anginal	26	37
Inadequately described	2	2
Respiratory manifestations:		
Pulmonary signs	50	67
Cyanosis	36	54
Dyspnea	43	50
Cough	38	45
Tachypnea	38	43
Hemoptysis	29	34
Pleural friction rub	12	12
Signs of infection:		
Fever	69	84
Chills	4	5
Cardiovascular manifestations:		
Tachycardia	53	62
Fall in blood pressure	27	35
Cold clammy skin	22	30
Apprehension	14	14
Arrhythmia	7	7
Distended veins in the neck	5	5
Rise in blood pressure	2	2
Palpitation	1	1
Systolic pulmonic murmur	1	1
Pulmonary gallop rhythm	1	1
Pericardial friction rub over pulmonic area	1	1
Cerebral manifestations:		
Coma	10	11
Sudden weakness	10	11
Syncope	6	6
Incontinence	3	3
Dizziness	3	3
Convulsions	2	2
Miscellaneous signs and symptoms:		
Jaundice	5	5
Nausea	2	2
Vomiting	2	2
Epigastric distress	1	1
Hiccup	1	1
Muscular aches and pains	1	1

1. *Pleurisy.*—Pleuritic pain occurred sixty-six times in 54 patients. There were no other symptoms or signs, with the exception of fever, in fourteen episodes, so that a diagnosis of simple pleurisy might have been made. Hemoptysis without additional evidence except pain was present in 9 other patients. Signs of pulmonary consolidation were found in the remaining patients with pleuritic pain, the clinical picture being that of pneumonia. The development of pleural effusion was noted in 1 case. One patient had both pleuritic and anginal pain in the same episode.

TABLE 2.—*Laboratory Observations*

Laboratory Test	Number of Times Test Performed	Number with Abnormal Results	Number with Normal Results
White blood cell count	92	65	27
Icterus index	24	11	13
Electrocardiogram	33	26*	7

* In 16 cases there was the classic pattern of acute cor pulmonale,[6] and in 10, minor changes consistent with an incomplete pattern of acute cor pulmonale.

2. *Pneumonia.*—Signs consistent with pulmonary consolidation were found sixty-seven times in 59 patients. Although in some of these the signs were equally consistent with a diagnosis of atelectasis, the high incidence of pleuritic pain (forty-three episodes) and hemoptysis (sixteen episodes) would more logically suggest a diagnosis of pneumonia. In this group vascular collapse was noted five times, clinical jaundice once and syncope once.

TABLE 3.—*Syndromes Simulated by Pulmonary Embolism*

Syndrome		Number of Episodes (Total 162)
1. Pleurisy		24
	Simple pleurisy 14	
	Pleurisy with hemoptysis 9	
	Pleurisy with effusion 1	
2. Pneumonia		80
3. Acute heart failure		12
	Dyspnea 4	
	Pulmonary edema 8	
4. Disease of the coronary arteries		39
	Angina pectoris 14	
	Acute myocardial infarction 25	
5. Acute vascular collapse		15
6. Disease of the central nervous system		3
7. Paroxysmal rapid cardiac action		1
8. Fever of unknown origin		3
9. Sudden death		3
10. Incidental observation at autopsy		3

3. *Acute Heart Failure.*—Forty-three patients had fifty episodes of dyspnea; this was the most prominent feature in twelve episodes, in four being identical with the paroxysmal dyspnea as seen in patients with heart disease and in eight being associated with pulmonary edema.

4. *Coronary Heart Disease.*—Anginal pain occurred thirty-seven times in 26 patients. The character of the pain and the absence of other symptoms suggested the diagnosis of angina

pectoris in fourteen episodes, whereas the character of the pain and the associated fever, shock, dyspnea or cyanosis suggested the presence of acute myocardial infarction in twenty-three episodes. Two additional cases in which adequate description of the pain in the chest was not available presented other features which suggested the diagnosis of acute myocardial infarction.

5. *Vascular Collapse.*—Vascular collapse (shock) was present in forty-two clinical episodes, in fifteen being the only clinical manifestation. Associated phenomena in the other 27 cases were pulmonary edema in 3, the clinical picture of acute myocardial infarction in 18, of pneumonia in 5 and manifestations referable to the central nervous system in 1.

6. *Manifestations Referable to the Central Nervous System.*—Eleven clinical episodes were characterized by sudden loss of consciousness. In six episodes the picture was that of syncope, but in five of these subsequent evidence suggested the diagnosis of angina pectoris, pneumonia or acute vascular collapse. Of the 5 remaining cases 2 showed additional signs (such as convulsions) leading to the clinical impression of a cerebral vascular accident.

7. *Paroxysmal Rapid Cardiac Action.*—Tachycardia occurred sixty-two times in 53 patients. In 7 of these the rhythm was irregular. This phenomenon was present either as the sole clinical feature of an episode (1 case) or in conjunction with one or more of the other manifestations already described.

8. *Fever of Unknown Origin.*—Fever of variable duration was the sole clinical manifestation of pulmonary embolism in 3 patients and for 1 of these the diagnosis of pulmonary embolism was first made at autopsy.

9. *Sudden Death.*—Sudden death, without the prior recognition of any symptoms or signs, occurred in only 3 patients.

10. *Incidental Observations at Autopsy.*—Unsuspected pulmonary embolism was found at autopsy in 3 patients who died of other causes.

COMMENT

The clinical course of pulmonary embolism is punctuated by a series of events, and in the intervals between these there may be a complete absence of abnormal signs. These events may be thought of as attacks or clinical episodes consisting of the sudden appearance of one or more symptoms (tables 1 and 3) with or without abnormal physical or laboratory signs. The peculiar combination of these symptoms or signs or the sudden appearance of a single one may result in the diagnosis of angina pectoris, syncope, paroxysmal rapid cardiac action and so forth. Clinicopathologic correlation has shown, contrary to our expectation, that each episode does not necessarily represent a separate pulmonary embolism. One embolus may be associated with repeated clinical episodes, or there may be fewer clinical episodes than the number of emboli which can be recognized at autopsy. The explanation for this discrepancy is not available, but possibly it may be found in reflexes arising from inflamed veins or in arteries lodging emboli.

Fatal pulmonary embolism uncommonly occurs without previous signs or symptoms, and the data clearly show that the source of emboli in the great majority of cases is the peripheral venous system (table 4). In order to prevent fatal embolism by the application of therapeutic measures that are or may become available, it is necessary to recognize the significance of the numerous warning symptoms or signs. The diagnosis should be made, or at least suspected, even though the only manifestations of pulmonary embolism are such common events as paroxysmal rapid cardiac action or what appears to be syncope. Pleuritic pain, especially in association with other manifestations, may indicate the correct diagnosis, but anginal pain, so common in pulmonary embolism, may be misleading and obscure the diagnosis. The data indicate that anginal pain occurs more commonly in association with pulmonary embolism than has been recognized. It is a good rule to consider seriously pulmonary embolism, in addition to other conditions, whenever a diagnosis of myocardial infarction is made but not firmly established. Early in the course of myocardial infarction the temperature is normal, whereas in pulmonary embolism it is elevated, as a rule, with the onset of pain. Brief episodes of syncope or vascular collapse are much more common before the onset of pain in pulmonary embolism than in myocardial infarction. Intensification of pain by in-

TABLE 4.—*The Source of Embolism*

Source	Number of Cases	Evidence
Veins of the leg	60	Definite evidence of thrombophlebitis
	30	Presumptive (no clinical mention of thrombophlebitis and no heart disease)
Veins of the arm	2	Definite evidence of thrombophlebitis
Pelvic veins	5	Postmortem evidence
	2	Suggestive clinical evidence
Mural cardiac thrombus	3	Postmortem evidence
	6	Suggestive clinical evidence of heart disease and no evidence of peripheral thrombophlebitis

spiration, with or without objective evidence of pleurisy, may occur with the outset of pain in pulmonary embolism but rarely occurs at a comparable stage in myocardial infarction. Anginal pain is apparently equally common in men and women with pulmonary embolism, in contrast to the sexual disparity in coronary heart disease. Anginal pain in pulmonary embolism may occur in patients without coronary heart disease or be absent in those with coronary heart disease, but almost one half of the patients in our series with anginal pain during pulmonary embolism had a past history of angina pectoris or acute myocardial infarction, and this fact may obscure the differential diagnosis. The incidence of anginal pain in pulmonary embolism is not influenced by the age of the patient.

Pulmonary embolism should also be considered in cases of pulmonary edema, sudden vascular collapse, cerebrovascular accidents and acute heart failure and as a possible diagnosis in cases of fever of unknown origin. Not infrequently a diagnosis of acute heart failure is made and pulmonary embolism is overlooked. The absence or paucity of signs in the heart and lungs in such cases should encourage one to elicit other signs and symptoms.

It is not necessary to consider the diagnosis of pulmonary embolism every time a patient faints or has a paroxysm of auricular fibrillation. Much depends on the background. Suspicion should be aroused, however, by these events in patients who have been immobilized by illness or operations and in those with histories of vascular disease or of trauma or infection, no matter how trivial in a leg (table 5). Homans [4b] has recently presented a series of cases of pulmonary embolism occurring in ambulatory patients from "silent" thrombosis of the veins of the leg. Unexplained vascular collapse, even if of short duration, should strengthen the suspicion of pulmonary embolism, particularly as more and more of the symptoms and signs listed in table 1 can be elicited. It is obvious that pain, dyspnea, tachycardia, fever, pulmonary signs and vascular collapse are common in pulmonary embolism, and hemoptysis is absent in many cases. Some of the manifestations of pulmonary embolism, such as pericardial friction rub or gallop rhythm over the pulmonic area, although uncommon, are of great importance in diagnosis and should be looked for carefully. Demonstration of a dilated pulmonary artery by physical examination or by roentgen examination may also aid in the diagnosis. When a diagnosis of pulmonary embolism is being considered on the basis of such simple events as paroxysmal auricular fibrillation or syncope, the definite presence of phlebitis greatly increases the probability that pulmonary embolism has occurred. But it is probably of greater importance that the diagnosis of pulmonary embolism should not be discarded merely because the presence of phlebitis cannot be established. Of the 108 cases studied here the source of embolism in 90 was presumably from thrombophlebitis of the deep veins of the leg. In only two thirds of these was there definite clinical evidence of an active phlebitic process. In a number of cases conclusive signs in the legs became apparent several days after the initial episode of pulmonary embolism, even though they were diligently searched for previously. In a number of cases peripheral thrombophlebitis was probably overlooked, because the legs of the patients were not examined daily. The possibility of phlebothrombosis occurring in the absence of thrombophlebitis [7] must also be considered and may explain the paucity of abnormal physical signs in the legs of patients who presumably have been having repeated pulmonary emboli from veins of the leg. In patients with heart disease or with changing rhythms the heart must be considered as a possible source of the embolism, and in patients who have had pelvic operations thromboses may develop in the pelvic veins from which clots may break off. Demonstration, therefore, of a possible source of embolism is strong evidence for pulmonary embolism, but the absence of any demonstrable source, especially of perpiheral thrombophlebitis, does not necessarily rule it out. From a statistical point of view it is probably correct to say that a diagnosis of peripheral phlebitis should be made when pulmonary embolism has been diagnosed, irrespective of signs in the legs, and from a therapeutic point of view it is important to realize that the phlebitis is often bilateral.

TABLE 5.—*Factors Predisposing to Embolism*

Predisposing Factor	Number of Cases
Operation	64
Nonsurgical diseases	14
Trauma to an extremity	6
Thrombophlebitis in patients with peripheral vascular disease	24

Laboratory studies may be of considerable help in diagnosis when considered in conjunction with the clinical picture. Abnormal roentgenograms are commonly found but require expert knowledge for proper interpretation. The absence of

7. Ochsner, A., and DeBakey, M.: Thrombophlebitis and Phlebothrombosis, South. Surgeon **8**:269, 1939.

confirmatory roentgenographic evidence does not rule out pulmonary embolism, because infarction may not have occurred or, if present, may be located in an area of the lung not accessible to adequate examination. The electrocardiographic pattern of acute cor pulmonale is distinctive, and if electrocardiograms are taken early and repeated at frequent intervals the number of cases in which definite help in diagnosis will thus be obtained will be considerably higher than one would anticipate on the basis of reports in the current literature. In this series the pattern of acute cor pulmonale was found in approximately 50 per cent of the cases in which electrocardiograms were taken. The white blood cell count is usually elevated after pulmonary embolism but not necessarily so, for in 30 per cent of the episodes in which this determination was made there was no leukocytosis. Slight elevation of the icterus index may be a clue leading to the diagnosis of pulmonary embolism. The laboratory thus aids greatly in making the diagnosis of pulmonary embolism, but embolism can occur in the absence of abnormal roentgenographic or electrocardiographic changes and without icterus or leukocytosis.

SUMMARY

One hundred and sixty-two episodes associated with pulmonary embolism in 108 cases were analyzed, and it was found that the total clinical picture simulated pneumonia, angina pectoris, acute myocardial infarction, pleurisy, vascular collapse or acute heart failure in a large percentage of the cases. In a much smaller group the clinical picture was that of fever of unknown origin, paroxysmal cardiac arrhythmia, cerebral vascular accident or syncope. The problem of differential diagnosis was studied.

Progress in Internal Medicine

BLOOD

A REVIEW OF THE RECENT LITERATURE

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In this review of the current literature on hematology up to 1945, an effort has been made to include foreign articles published during the past several years which have not heretofore been available in this country. Review of articles in more readily available publications is limited to those appearing during 1944, unless it has appeared that through oversight an important article has failed to receive attention in previous reviews. Although as comprehensive a coverage of the literature as possible has been attempted, limitations of personnel and facilities have made certain omissions inevitable. These, it is hoped, may be corrected in future reviews. It has been a source of surprise and gratification that in spite of the obvious obstacles to research so many significant investigative projects were successfully carried out both in this country and abroad.

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PERNICIOUS ANEMIA

Etiology.—It is stated by Castle[1] that beef muscle, milk, eggs, liver, yeast, rice polishings and wheat germ are known to contain the so-called extrinsic factor for the hemopoietic reaction with normal human gastric juice (the intrinsic factor). Using the technic which he has previously employed of testing material by incubating it with normal human gastric juice and administering the product to patients with pernicious anemia, he found that the careful purification required to render crude casein vitamin-free is also essential for the elimination of the extrinsic factor. Furthermore, it was observed that the addition of thiamine, riboflavin, nicotin-

1. Castle, W. B.; Ross, J. B.; Davidson, C. S.; Burchenal, J. H.; Fox, H. J., and Ham, T. H.: Extrinsic Factor in Pernicious Anemia: Ineffectiveness of Purified Casein and of Identified Components of the Vitamin B Complex, Science **100**:81, 1944.

amide, pyridoxine hydrochloride, dicalcium pantothenate, paraaminobenzoic acid, choline hydrochloride, *i*-inositol, biotin, xanthopterin and folic acid to casein so extracted gave no evidence of the reconstitution of the extrinsic factor activity of the crude casein. He concluded, however, that it is nevertheless reasonable to continue to regard the extrinsic factor as the thermal stable component of the vitamin B complex, as yet unidentified.

The theory has previously been advanced by Agren [2] that the intrinsic factor of Castle might be identical with the enzyme aminopolypeptidase. This is based on the observation that the injection of crystalline secretin intravenously into cats provoked a secretion from the distal part of the pyloric region and the proximal part of the duodenal region which contained a high concentration of aminopolypeptidase. It was demonstrated further that an enzymic action (proteolysis) took place after this secretion was incubated with muscle extract. Furthermore, while preparing the enzyme from the pyloric mucosa of hogs it was found that purified enzyme solutions apparently contain most of the intrinsic factor activity present in the mucous membrane. The author states he has now purified the enzyme to about a hundred times. Evidence that the aminopolypeptidase is the intrinsic factor is based on the assumption that if the intrinsic factor activity can be shown to parallel that of aminopolypeptidase the conclusion that the latter may be identical with the intrinsic factor would be favored. While this may be suggestive evidence, it certainly would not be entirely convincing. Clinical results which the investigator obtained on 4 patients suggested this relation. He states that a detailed report will appear in the *Acta Medica Scandinavica.*

Careful consideration is given by Askey [3] to the hypothesis that pernicious anemia may be of dietary origin. The rather startling statement is made that if dietary deficiencies cause addisonian pernicious anemia then they must also explain the natural distribution and natural history of the typical form of the disease. This is a conclusion which in our minds does not seem to be entirely permissible. In evaluating the relation of the dietary factors in patients with pernicious anemia, Askey sets up rather high standards as diagnostic criteria. For example, the diagnosis of pernicious anemia is not absolutely acceptable to him unless there is a primary composite triad of essential criteria consisting of (1) a permanent histamine-refractory anacidity, (2) a permanent reduction of Castle's intrinsic factor and (3) a reduction of the stored anti-pernicious-anemia principle. While his arguments favoring the rigidity of the criteria in evaluating patients with macrocytic anemia are undoubtedly sound, nevertheless, they are not practical. Askey considers that the natural history of pernicious anemia is indicated by an orderly development of anacidity, loss of intrinsic factor and loss of anti-pernicious-anemia liver principle. While this theory may be correct, it certainly is an assumption. He cites convincing evidence to indicate that there is no relation between the natural distribution of the disease and poor nutrition. For example, in China and Java, where malnutrition is common, pernicious anemia is almost unknown. He also states that, although no precise data regarding the diets of patients with pernicious anemia over long periods are available, there is no evidence to indicate that there is an inadequate intake of food except in the periods just before the manifestations of the disease appear. We have been interested in this problem since 1927 and made an extensive analysis, which was not published, of the dietary habits of a fairly large group of patients with pernicious anemia and compared this with a similar analysis of a control group with various other diseases. There was no difference between the two groups. In discussing the question "can dietary deficiencies produce addisonian pernicious anemia?" Askey [4] cites the prevalence of macrocytic anemia in many Mohammedan women of India, who live on diets largely vegetarian, high in carbohydrate and low in protein and in natural vitamins of the B complex. As this type of anemia does not respond to purified Dakin-West anti-pernicious-anemia fraction (Anahaemin), he concludes that it apparently is not due to a deficiency of specific anti-pernicious-anemia principle. Likewise, concerning sprue, he states that hydrochloric acid is often found in the gastric juice and that the intrinsic factor may also be present. It apparently is his opninon that dietary deficiencies cannot produce characteristic addisonian pernicious anemia. Although he agrees that tropical macrocytic anemia, pellagra and sprue respond to the injection of liver extract, he objects to the acceptance of this information as proof that these diseases are identical with addisonian pernicious

2. Agren, G.: Nature of the Anti-Anaemic Factor (Castle), Nature, London **154**:430, 1944.

3. Askey, J. M.: Dietary Factor in Etiology of Pernicious Anemia, Ann. Int. Med. **21**:402, 1944.

4. Askey, J. M.: Addisonian Pernicious Anemia Without Achlorhydria: Does It Exist? Gastroenterology **2**:1, 1944.

anemia. He rejects it because, he claims, the Cohn fraction G liver extract is usually employed in the treatment of such patients and this contains two distinct anti-macrocytic-anemia principles, namely (1) the specific pernicious anemia principle and (2) the anti-macrocytic-anemia principle effective against tropical macrocytic anemia. In brief, Askey concludes that deficient diets in human beings over a period of years may produce macrocytic anemias but not commonly the mechanism operative in addisonian pernicious anemia. In a survey of the literature relating to the production of the essential features of pernicious anemia in experimental animals by dietary deficiency, Askey concludes that only in hogs has the essential triad of objective signs been produced by a defective diet. He concludes that such a condition has been produced by Miller and Rhoads.[5] It is his opinion, however, that dietary deficiencies which produce the essential objective triad of pernicious anemia in members of a remote species, hogs, fail to produce pernicious anemia either in members of the nearest related species to human beings, monkeys, or in human beings themselves. He does not regard these experiments, therefore, as being of crucial significance.

In a discussion of the racial distribution of pernicious anemia, Askey concludes that when the racial factor is constant in any particular area of the world and the climatic factor is variable varying results occur. It is his opinion, therefore, that climate is of secondary importance to race in producing the incidence of pernicious anemia. He believes that racial factors best explain the natural geographic distribution of the disease. It is his final opinion that the natural distribution, which is racial, geographic and climatic, can be adequately explained by hereditary factors.

A résumé of the literature dealing with the late effects of total and subtotal gastrectomy has been given by Ingelfinger.[6] Various aspects of disturbed physiologic function following removal of the stomach are considered by Ingelfinger, but only those relating to the development of anemia will be discussed here.

He asks: "Why do not patients with gastrectomies, particularly those with total gastrectomies, have pernicious anemia?" He goes on to say, however, that as a matter of fact a small number of patients do, but in his opinion the development of true pernicious anemia is an extremely rare sequela. He points out, however, that in 1941 Meyer, Schwartz and Weissman[7] collected 54 cases of what they considered to be authentic pernicious anemia following total gastrectomy. Since that time another case has been reported by Rhodes and Grunberg.[8] It is pointed out by Ingelfinger that before one can assert that true pernicious anemia occurs as a sequel to gastrectomy control periods during which the patient receives extrinsic factor and is observed by means of reticulocyte counts before and during liver therapy, adequate follow-up periods and possibly even studies of the bone marrow are necessary. In his opinion, even if the evidence for pernicious anemia is unequivocal, the possibility still exists that in some cases pernicious anemia following gastrectomy is merely the results of coincidence. The relation of total gastrectomy to the development of the blood picture of pernicious anemia has been of interest to us over a considerable period of years. Certainly, if the hypothesis of Castle is true, then the removal of the entire stomach should be followed by the development of a blood picture of pernicious anemia. This undoubtedly occurs in some cases, but it sometimes does not appear until after a period of two to four years has elapsed. When one considers that the operation for total gastrectomy is even now not a common one, but is becoming more so, and that in the past many of the patients did not survive the operation over a few days and some not over a few months, it is not surprising that only a relatively small number of cases can be recorded. It is our tentative belief, which may be revised depending on the subsequent observations, that the complete removal of the stomach of any human being will ultimately be followed by the development of the blood picture of pernicious anemia if the patient is followed over a period of years and does not receive anti-pernicious-anemia therapy. With the increasing frequency of this operation, the answer to this important question should be learned within the next few years.

A report on total gastrectomy of 73 patients, of whom 24 failed to survive, giving an operative mortality of 33 per cent, is published by Lahey

5. Miller, D. K., and Rhoads, C. P.: The Experimental Production of Loss of Hematopoietic Elements of the Gastric Secretion and of the Liver in Swine with Achlorhydria and Anemia, J. Clin. Investigation **14**: 153, 1935.

6. Ingelfinger, F. J.: Late Effects of Total and Subtotal Gastrectomy, New England J. Med. **231**:321, 1944.

7. Meyer, K.; Schwartz, S. O., and Weissman, L. H.: Pernicious Anemia Following Total Gastrectomy, Arch. Surg. **42**:18 (Jan.) 1941.

8. Rhodes, A. J., and Grunberg, A.: Macrocytic Anemia Following Partial Gastrectomy, Brit. M. J. **1**: 726, 1943.

and Marshall.[9] Of the last 28 patients on whom gastrectomy was done, however, only 5 died, which figure represents a mortality rate for that group of 18 per cent. It is undoubtedly true that total gastrectomy for gastric carcinoma will become a more common operation in the future as an increasingly large number of patients are being reported on on whom this operation has been performed. This is of special interest to the hematologist, as it creates an experimental condition which should throw considerable light on Castle's hypothesis in relation to the etiologic importance of the intrinsic factor of the stomach to the development of pernicious anemia. A brief reference is made in this paper to the appearance of anemia following the operation, the sole statement being: "In spite of the loss of all the gastric tissue, the primary type of anemia has not been encountered after total gastrectomy. Postoperative secondary anemia is a frequent complication to be watched for, and, when it does occur, the patient should be put on a regular maintenance dose of liver extract parenterally." The increasing frequency of gastrectomy, therefore, raises an interesting question which will undoubtedly be decided by further observations: Why does not complete anatomic extirpation of the stomach, which is responsible for the formation of the intrinsic factor, always produce pernicious anemia? This question is asked by Askey.[4] It is known that patients may survive for years following total gastrectomy without the development of pernicious anemia. Allen [10] reported on 1 patient alive and well with a normal blood picture four and one-half years after total gastrectomy. It would seem that if the stomach is the site of the manufacture of the intrinsic factor after its removal there must be either a large store of this material or of the erythrocyte-maturing factor somewhere in the body. Another possibility is that the intrinsic factor may be manufactured elsewhere, although with the present state of knowledge there is no information which has a bearing on this particular point. It has been shown by Geiger, Goodman and Claiborn [11] that total gastrectomy in swine produces exhaustion of the supply of anti-pernicious-anemia principle in the liver. Now information bearing on this point is available in human beings who had a total gastrectomy some years ago. Certainly, if the opportunity offers, this observation should be obtained.

A comprehensive review of the literature relating to the stomach and erythropoiesis and also to the etiologic role played by the stomach in producing both hypochromic and hyperchromic anemias is given by Wollheim.[12] In addition, he presents some of his own experimental observations on rabbits and dogs and discusses his conclusions relating to the etiology of pernicious anemia and to the normal control of erythropoiesis.

Achlorhydria in Pernicious Anemia.—When one reports a case of pernicious anemia in which it is claimed that hydrochloric acid is present in the gastric juice, it becomes necessary, in the opinion of Askey,[4] first, to exclude all the possible causes of macrocytic anemia; second, to demonstrate the absence of the intrinsic factor, and, finally, to prove that the anemia is due to a deficiency of the specific anti-pernicious-anemia liver factor. Cirrhosis of the liver, extreme hypothyroidism, pregnancy, sprue, pellagra, gastric neoplasm, intestinal strictures and anastomoses and gross nutritional deficiencies are all adequate causes for macrocytic anemia. These must be excluded before the diagnosis of true pernicious anemia is acceptable. According to Askey, a reduction in the gastric intrinsic factor may be associated with pregnancy, gastric neoplasm, sprue, intestinal strictures, ulcers and avitaminosis, and the mechanism of the loss of the intrinsic factor in these conditions is not the same as in addisonian pernicious anemia. To be significant, therefore, the loss of the intrinsic factor must be shown to be idiopathic by the exclusion of the other conditions which may induce it. It is recognized by Askey that it is impracticable to demonstrate reduction in the specific liver principle. Direct studies by biologic assay of the liver can be made only in the fatal cases. Indirect data obtained by the response of the patient to the administration of liver extract are not entirely acceptable, according to this investigator. In his opinion, the liver extract usually used is Cohn's fraction G, which contains not only the specific anti-pernicious-anemia principle but also different fractions which have been shown to be effective in nutritional macro-

9. Lahey, F. H., and Marshall, S. F.: Indications for and Experience with Total Gastrectomy, Based on Seventy-Three Cases of Total Gastrectomy, Ann. Surg. **119**:300, 1944.

10. Allen, A. W.: Total Gastrectomy for Carcinoma of Stomach, Am. J. Surg. **40**:35, 1938.

11. Geiger, A. J.: Goodman, L. S., and Claiborn, L. N.: Effects of Gastro-Intestinal Resections in Swine on Anti-Anemia Potency of Liver, with Observations on Nature and Sources of Materials Effective in Pernicious Anemia, Yale J. Biol. & Med. **13**:259, 1940.

12. Wollheim, E.: Magen und Erythropoese, Schweiz. med. Wchnschr. **73**:233, 1943.

cytic anemia of the tropics. According to him, it is impossible to know, therefore, whether improvement of a macrocytic anemia following the administration of Cohn's fraction G is due to the specific anti-pernicious-anemia fraction or the fraction effective against nutritional macrocytic anemia. He suggests that if the response to liver is used as a therapeutic test a favorable effect is of little significance unless the Dakin-West product or one of the other highly purified fractions obtained from the original Cohn's fraction G is used. He assumes that a determination of the response to desiccated hog stomach (Ventriculin) would be a more precise and accurate therapeutic test.

In a consideration of 47 reports in the literature of cases of pernicious anemia without achlorhydria, he has concluded that 32 of these cases are unacceptable because other causes for the anemia were present or because the data were unconvincing. It is his final opinion that it has never been established beyond doubt that addisonian pernicious anemia can exist with persistence of secretion of hydrochloric acid. The diagnosis of addisonian pernicious anemia, therefore, without achlorhydria has been a presumption, not an established fact. It is his opinion that the existence of true pernicious anemia without anacidity as yet cannot be accepted. In this belief we are in complete accord. Certainly, the presence of hydrochloric acid in the gastric secretions of patients suspected of having pernicious anemia casts serious doubt on the diagnosis, and some other explanation of the associated macrocytic anemia should be sought.

A gastric analysis was done on 418 general medical patients in Bombay, India, by Bhende,[13] and it was found that 84 of them had achlorhydria. Seventy-nine of these patients had anemia, and hence it was apparent that the anemia contributes most frequently in this particular area to achlorhydria. These patients, in fact, were admitted to the hospital primarily for treatment of the anemia state. Analysis of the types of anemia are as follows: true achlorhydria, as indicated by the absence of free hydrochloric acid following the injection of histamine, 44; pernicious anemia, 19; tropical macrocytic anemia, 13; idiopathic hypochromic anemia, 5; normocytic anemia of varied origin, 4; hook worm infection, 1; pellagra, 1, and carcinoma of the stomach, 1. There were 35 patients classified as having false achlorhydria, that is, patients who had no free hydrochloric acid after a test meal. Of these patients, 7 secreted acid after the administration of dilute alcohol and the remainder required the maximum stimulus of histamine for the demonstration of hydrochloric acid. Thus, in 28 of 72 patients with anemia, or 38.8 per cent, acid was found in the gastric contents only after the injection of histamine. There were 31 patients with false achlorhydria, classified as tropical macrocytic anemia; 1 with idiopathic hypochromic anemia; 2 with normocytic anemia of varied origin, and 1 with normocytic anemia with cirrhosis of the liver. The author emphasizes that histamine stimulus must always be employed to distinguish true from false achlorhydria. He also points out that some patients with tropical macrocytic anemia do not exhibit true achlorhydria.

A comprehensive consideration of achlorhydria in patients with anemia is given by Moschcowitz.[14] He discusses the incidence of achlorhydria in apparently normal persons, and the relation of achlorhydria to idiopathic hypochromic anemia, to pernicious anemia, to the anemia of pregnancy, to the anemia of myxedema, to the anemia of sprue and to the anemia of gastric carcinoma. A statement is made which we challenge, namely, that pernicious anemia may develop in persons with hydrochloric acid in the stomach. The reference to the work of Askey abstracted in this review is of interest in this connection. The discussion by Moschcowitz, however, is exceedingly thorough, and a bibliography of fifty-eight articles is appended.

It has been reported by Davis [15] that the daily oral administration of 5 Gm. of soybean lecithin to dogs resulted in a reduction in the red blood cell count which persisted for at least ten days after cessation of the lecithin feeding. He also observed that choline hydrochloride in daily oral doses of 8 mg. per kilogram of body weight caused a significant depression in the number of erythrocytes in dogs. The action of choline in this case was explained by its assumed depressing effect on erythropoiesis caused by the increased blood flow and oxygen supply to the bone marrow through its vasodilator action.

Studies have also been made by Davis [16] which, if verified, would provide a mechanism for the

13. Bhende, Y. M.: Achlorhydria and Anaemia: An Analysis of Seventy-Nine Cases, Indian M. Gaz. **77**:13, 1942.

14. Moschcowitz, E.: Essays on the Biology of Disease: The Biology of Achlorhydria in Relation to Anemia, J. Mt. Sinai Hosp. **10**:796, 1944.

15. Davis, J. E.: Depression of Normal Erythrocyte Number by Soybean Lecithin or Choline, Am. J. Physiol. **142**:65, 1944.

16. Davis, J. E.: Experimental Production of Hyperchromic Anemia in Dogs Which Is Responsive to Anti-Pernicious Anemia Treatment, Am. J. Physiol. **142**: 402, 1944.

evaluation of anti-pernicious-anemia medication. He produced a hyperchromic anemia in dogs by the oral administration of three doses daily of choline chloride, 10 mg. each per kilogram of body weight. This resulted in moderate to mild anemia in the animals. He believed that the anemia was the result of a depression of erythropoiesis. It is of great interest to note that the intramuscular injection of adequate doses of purified solution of liver extract in 3 of the dogs caused an increase in the number of red blood cells, with a return to normal in approximately four weeks. These responses continued in spite of administration of choline. Powdered stomach U. S. P., fed in daily doses of 20 Gm. to 1 mildly anemic dog, caused a return of the red blood cells and hemoglobin percentage to normal within twelve days in spite of continued choline feedings. These experiments, if confirmed, are of the greatest importance and deserve careful consideration by all hematologists.

Davis [16] gave 60 Gm. of lard and 10 mg. of choline hydrochloride per kilogram of body weight daily to 4 normal dogs and observed the effect on the circulating blood. He found that there was a rapid significant reduction in the erythrocyte count, associated with an elevation of the icterus index. It was his opinion that the fat caused anemia by increasing hemolysis and that the choline feeding alone would not produce a significant fall in the erythrocytes until it had been administered for eight or more days. It was his belief that the choline acted by causing vasodilatation and improved blood and oxygen supply to the bone marrow, thus depressing erythropoiesis. As he expressed it: "Choline acted as a weak brake to inhibit any acceleration of erythropoiesis which may normally follow the hemolytic destruction of red blood cells."

It has been noted by Johnson, Freeman and Longini [17] that the lacteal lymph collected close to the small intestines of dogs after a fatty meal is strongly hemolytic. They assumed that the hemolytic action was due to the action of free fatty acids which had failed to be resynthesized. This observation led to a series of experiments in which they demonstrated that exposure of normal human red blood cells to lipemic serum renders those cells more susceptible to hemolysis by distilled water or by soap solutions. They concluded, therefore, that these experiments suggest that the destruction of an appreciable part of red blood cells in normal human beings might be accounted for by the injurious effects of ingestion of fat, although bone marrow seems fully able to compensate for these losses of red blood cells. It occurred to them, however, that an increase in this destructive effect of ingested fat might be responsible for certain human anemias. After making a number of observations on patients with pernicious anemia, they concluded that in patients with untreated pernicious anemia the ingestion of fat is more injurious to red blood cells than it is in treated patients with pernicious anemia or in normal persons. Their experiments also led them to conclude that the fragility of the erythrocytes is increased by exposure to normal lipemic serum. These observations strongly suggested to the observers that the ingestion of fat may injure the red blood cells sufficiently to contribute significantly to the anemia of pernicious anemia and that an abnormal sensitivity of the red blood cells to the products of fat absorption may be an etiologic factor in this type of blood disorder. The authors review the evidence supporting the concept that hemolysis is at least a factor in causing the anemia of pernicious anemia and state that evidence is accumulating to the effect that liver extract acts in anemia generally by protecting the erythrocytes from excessive hemolysis. They also note that liver therapy has been demonstrated to protect red blood cells against hemolysis and also to be curative in the anemia produced in animals by indole plus a deficient diet. This fact is supported by their experimental evidence that ingestion of fat injured the red blood cells in patients with untreated pernicious anemia more than in normal persons or in patients with treated pernicious anemia. It is their opinion that the evidence presented in this paper would seem to provide a basis for attempts to control or improve the condition of patients with pernicious anemia by a diet that is as nearly fat-free as possible.

These observations are of interest and open up a new field which may be of great importance and have a significant bearing on the cause of pernicious anemia as well as the cause of other types of hemolytic anemia.

Previous literature dealing with the possible association between the relative lack of solar radiation and the mortality rate from pernicious anemia is reviewed by Thiersch.[18] It has been stated that there is a significant relation between the relative lack of solar radiation and the mor-

17. Johnson, V.; Freeman, L., and Longini, J.: Erythrocyte Damage by Lipemic Serum in Normal Man and in Pernicious Anemia, J. A. M. A. **124**:1251 (April 29) 1944.

18. Thiersch, J. B.: Solar Radiation and Pernicious Anemia in South Australia, M. J. Australia **1**:583, 1944.

tality rate from pernicious anemia in the United States and that this is also true concerning the disease in Europe. Furthermore, in 1942 Apperly [19] came to the conclusion that the mortality rate of pernicious anemia and the amount of solar radiation were inversely related. The studies by Thiersch, however, do not confirm this view. He concludes that there was no evidence found in South Australia to confirm the hypothesis that an inverse relation existed between the incidence of pernicious anemia and the degree of solar radiation. While the number of cases of pernicious anemia in South Australia corresponds closely to that in England, in relation to the population, the occurrence of cutaneous cancer in South Australia is far greater than that in the British Isles. The increase is due mainly to the greater solar radiation, as the localization of the cutaneous cancers on the face and hands indicates.

It is emphasized by Jasinski [20] that the condition of the bone marrow in both patients with sprue and patients with pernicious anemia is identical. Furthermore, this investigator states that in the presence of an iron deficiency anemia the fully developed picture of pernicious anemia may be inhibited.

The Diagnosis of Pernicious Anemia.—It is stated by Rossi [21] that many cases of pernicious anemia do not present the classic clinical picture but often have a vague symptomatology. He presents as an example the following clinical forms, all of them atypical: (1) febrile, (2) septicemic, (3) intestinal, (4) gastric, (5) jaundiced, (6) nervous. In each one of these forms, he states, the diagnosis of pernicious anemia was made after a study of the blood and the bone marrow.

A case of a 20 year old youth who was said to have had pernicious anemia is discussed by Carrera Dominguez.[22] In this case the most outstanding features of the clinical history were those referred to the gastrointestinal tract, namely, vomiting, great loss of weight, sore tongue and a tendency to diarrhea. Physical examination showed pallor, mitral stenosis and slight splenomegaly. The red blood cell count was 1,380,000 per cubic millimeter and the color index 1.63. The white blood cell count was 3,200 per cubic millimeter. The serum bilirubin level was 1.6 mg. per hundred cubic centimeters of serum. There was achlorhydria present. The patient made a good recovery with liver therapy. The author describes this case because of the outstanding complaints referable to the gastrointestinal systems. He gives a brief discussion of the presence of such symptoms in patients with pernicious anemia.

A general article dealing with the clinical picture and the diagnostic points of pernicious anemia is presented by McNamara.[23]

The Nervous System in Cases of Pernicious Anemia.—The clinical and pathologic observations in 2 cases of pernicious anemia with subacute degeneration of the brain and spinal cord are described by Adams and Kubik.[24] They emphasize that the cause of the degeneration of the nerve fiber in such cases is obscure but suggest that a deficiency of some substance other than the intrinsic factor may account for it. It is also pointed out that lesions involving the cerebrum are less well known than are the changes in the spinal cord and that they are not even mentioned in many textbooks on neurology. In each of their 2 cases there were well defined neurologic and psychiatric symptoms, which serve as a basis for their discussion. In their opinion the lesions of the cerebrum and of the spinal cord are almost exactly alike and consist of diffuse, although uneven, degeneration of the white matter with little or no proliferation of the fibrous glia. This similarity suggests that the degeneration of the cerebral white matter is specifically related to pernicious anemia as is subacute combined degeneration of the spinal cord. The neurologic changes which occur in patients with pernicious anemia are unique and quite unlike those that are present in patients with cerebral vascular disorders, multiple sclerosis, encephalitis and other more chronic degenerative diseases. They differ from those observed in pellagra, because in the latter condition, although there is degeneration in the columns of Goll throughout their course, this process is not uneven as in pernicious anemia and because in pellagra there is a pronounced gliosis. The authors point out an interesting sequence of events which has been observed by us on more than one occasion. In their opinion the changes

19. Apperly, F. L.: Relation of Pernicious Anemia to Solar Radiation in Skin Cancer, Am. J. M. Sc. **203**: 854, 1942.

20. Jasinski, B.: Das Verhalten des retikuloendothelialen System des Knochenmarkes bei der Perniziosa- und Sprue-Erythropoese, Schweiz. med. Wchnschr. **74**: 188, 1944.

21. Rossi, R.: Formas disimuladas de anemia perniciosa, Rev. argent.-norteam. cien. méd. **1**:343, 1943.

22. Carrera Domínguez, P.: Notas hematologicas con motivo de un caso de anemia de Biermer, Medicina, Madrid (pt. 2) **11**:77, 1943.

23. McNamara, F. P.: The Clinical Diagnosis of Pernicious Anemia, J. Iowa M. Soc. **34**:242, 1944.

24. Adams, R. D., and Kubik, C. S.: Subacute Degeneration of Brain in Pernicious Anemia, New England J. Med. **231**:1, 1944.

in the spinal cord usually, if not invariably, precede the changes in the brain; in fact the order of development of involvement of the central nervous system is as follows: first the posterior columns, then the lateral and anterior columns and finally the cerebral white matter. They refer to an interesting article by Bertrand and Ferraro [25] in which it is reported that in a patient with gastric carcinoma and macrocytic anemia there were lesions of the brain and spinal cord exactly similar to those observed in patients with pernicious anemia. They cite such a case as an example of the fact that subacute degeneration may be associated with conditions other than pernicious anemia. Although there is a difference of opinion about this matter as expressed in various articles in the literature, they believe that patients with lesions of the brain have mental symptoms, whereas the converse is not necessarily true, as cerebral lesions have not always been found in patients with mental symptoms. They conclude by stating that they favor the supposition that both subacute combined degeneration of the spinal cord and subacute degenerative lesions of the brain represent an advanced stage in a specific process that is induced by a deficiency of certain substances necessary to the metabolism of myelinated nerve fibers. They do not think that every patient with pernicious anemia will have demonstrable lesions of the brain, but it is their belief that all those in whom there are definite and widely disseminated lesions of the brain will probably have mental disorders.

Other Diseases Associated with Pernicious Anemia.—Two cases of thyroid dysfunction associated with pernicious anemia are reported by Charaton.[26] One patient was a woman of 62 years who had a nodular goiter with severe anemia which had all the characteristics of pernicious anemia. This responded to treatment with crude liver extract and later with desiccated hog stomach. The thyroid condition was treated with strong solution of iodine U. S. P. (Lugol's solution). The patient improved strikingly, and the red blood cell count came to normal. Thyroidectomy was refused. The second patient was a woman of 68 years who, he says, had the classic features of myxedema, although no basal metabolic rate or cholesterol estimation was reported. There was no question that she had a severe anemia with a red blood cell count of approximately 1,400,000 and a hemoglobin content of 44 per cent. There was achlorhydria following the injection of histamine. With administration of desiccated thyroid, 1 grain (0.06 Gm.) twice daily, and crude liver extract, 2 cc. intramuscularly, striking improvement resulted. The question arises here as to whether she might not have had a severe macrocytic anemia of myxedema rather than pernicious anemia, although the two diseases have been reported previously as coexisting in the same patient. In such patients the elevation of the blood cholesterol may have been of importance, as it is always elevated in patients with myxedema in our experience.

According to Woolley [27] the term "leukanemia" was first introduced by Leube in 1900. It was considered to be a condition characterized by a leukemoid blood picture accompanied with a macrocytic hyperchromic anemia. It is likely, however, that leukanemia in the earlier literature indicated a condition which was usually an aleukemic leukemia or pernicious anemia with a leukemoid blood reaction. Woolley considers that the term does not designate a separate disease entity but is used for purely descriptive purposes and thus may be likely to give rise to confusion. The case of a patient who had pernicious anemia and in whom outspoken myelogenous leukemia later developed is reported by Woolley. This patient was first seen in 1932, at which time she was 48 years of age, and she then had the characteristic clinical picture of pernicious anemia. There was achlorhydria and a characteristic reticulocyte response to antipernicious-anemia medication. Ten years later the typical picture of chronic myelogenous leukemia developed, with a white blood cell count of 85,600 per cubic millimeter and characteristic immature white blood cells. In addition to the great increase in the white blood cell count and the presence of a high percentage of primitive leukocytes, there was enlargement of the spleen to about 6 inches (15 cm.) below the left costal margin. Roentgen ray therapy caused a reduction in the leukocytes and in the size of the spleen. It is possible that the two diseases may occur in the same patient as a result of a constitutional predisposition of the hemopoietic system. The author concludes, however, that the cause of the association of the two diseases in the same person is unknown but that the association probably is coincidental.

25. Bertrand, I., and Ferraro, A.: Contributo alla conoscenza dell'anatomia patologico della degenerazione sub-acuta combinata del midollo spinale, Cerebello **4**: 1, 1924.

26. Charaton, F. B.: Pernicious Anemia Associated with Thyroid Dysfunction: Two Cases, St. Thomas Hosp. Gaz. **42**:94, 1944.

27. Woolley, P. B.: Myelogenous Leukemia Complicating Pernicious Anemia, Lancet **1**:85, 1944.

MACROCYTIC ANEMIA RELATED TO PERNICIOUS ANEMIA

Two cases of deficiency anemia in infants are reported by Bass,[28] 1 of which was corrected by the use of liver extract and the other by hydrolyzed casein. It is emphasized by Bass that in the majority of instances severe anemia in early infancy is due to a deficiency of iron but that an anemia may be due also to an inadequate supply of other substances concerned with the production of hemoglobin. Bass states that the anemia has been described in some of the reports in the literature as macrocytic, resembling pernicious anemia in adults, and that in others the condition is described as being similar to a hypochromic anemia due to iron deficiency. He reports 1 case of its occurrence in a 6 month old infant with a red blood cell count of 920,000 per cubic millimeter and a hemoglobin content of 17 per cent. This anemia was refractory to iron but responded to injections of liver extract with an increase in the reticulocytes to 16 per cent and a rapid return of the hemoglobin content and red blood cell count to normal. The second case was that of a 5 month old infant who had a severe anemia which did not improve after long-continued treatment with iron and frequent blood transfusions. In this case, however, cure was obtained by the administration of hydrolyzed casein known to contain the essential amino acids. It is of interest to note that anemia developed in this infant at a time when goat's milk had been substituted for cow's milk on account of an allergy to the latter. A full discussion of the anemia associated with the diet of goat's milk is given.

It is pointed out by Davis[29] that pernicious anemia in the first two decades of life is an extremely rare condition. He cites reviews of the literature which include a survey of 1,532 cases of pernicious anemia, with only 4 of the patients being under 20 years of age. He doubts if any of the published cases of pernicious anemia in children have met the rigid diagnostic criteria of that condition. Nevertheless, he states that in a number of the cases the anemia was hyperchromic and macrocytic and responded to liver therapy. He considers this evidence that the anemias were megaloblastic in nature. Three cases of severe megaloblastic anemia in children 12, 13 and 14 years old were reported. The evidence in all 3 cases against a diagnosis of true addisonian pernicious anemia is the failure to respond typically to liver extract therapy, the presence of free hydrochloric acid in the gastric contents and the temporary nature of the blood condition. In conclusion Davis states that, although the blood and sternal marrow pictures were typical of pernicious anemia, there was convincing evidence against the acceptance of this diagnosis. In his opinion, the condition may have resulted from defective assimilation from the alimentary tract. It is of interest that 2 of the 3 patients in these cases responded to proteolyzed liver administered orally after it had been demonstrated that they were refractory to parenteral injections of liver extract of known potency.

It is reported by Seelig and Hemming[30] that Indian soldiers on field service in whom malaria developed were commonly found to have severe macrocytic anemia. The observations in 23 cases are summarized. They stated that the patients' skins were pale, with a lemon tint, and that the tongues were smooth, atrophic and suggestive of Hunter's glossitis in pernicious anemia. Studies were not made on the hydrochloric acid content of the gastric secretions. The livers and spleens were palpable in all patients but not greatly enlarged. Lymph nodes were normal. All patients came from a malarious area, and each had had fever with rigor within two or three months of his admission to the hospital or had malarial parasites (malignant tertian or benign tertian) in the blood when admitted. Patients had had no antimalaria treatment, or the treatment was inadequate or intermittent. Examination of the blood showed severe megalocytic anemia, with considerable anisocytosis and poikilocytosis, frequent punctate basophila, small and large nucleated red cells and leukopenia. All showed well defined hypochromasia. The serum bilirubin level did not exceed 1 mg. per hundred cubic centimeters in any case. The number of red cells averaged between 2,000,000 and 3,000,000 although in some instances the anemia was more severe. One patient was reported as having a red blood cell count of 560,000 per cubic millimeter. The authors considered that the anemia was probably of a nutritional macrocytic type which was precipitated by the inadequately treated malaria. Treatment was carried out with iron, liver and a full diet, and the results were satisfactory.

28. Bass, M. H.: Deficiency Anemia in Infants: Report of Two Cases with Associated Temporary Deficiency of Antianemia Factor in One and Allergy and Abnormal Digestion of Protein in the Other, Am. J. Dis. Child. **67**:341 (May) 1944.

29. Davis, L. J.: Macrocytic Anemia in Children, Arch. Dis. Childhood **19**:147, 1944.

30. Seelig, S. F., and Hemming, J. R.: Megalocytic Anaemia as a Sequel to Malaria, Lancet **1**:498, 1944.

Macrocytic anemia as it occurs in natives of New Guinea is reported on by Giblin.[31] He states that his notes, which cover the twenty years from 1921 to 1941, were written from the point of view of a casual clinical worker and from memory. The macrocytic anemia seen in natives of New Guinea is characterized by the following signs: (1) relatively acute onset with pyrexia, which may last weeks or months; (2) rapid enlargement of the spleen, which is both painful and tender but diminishes in size during spontaneous remission; (3) blood picture of macrocytic anemia; (4) rapid loss of weight, and (5) spontaneous remissions and relapses. He states that there is also a more chronic type of macrocytic anemia, in which the spleen is enlarged but not painful. The anemia is of low grade, is compatible with reasonably good health and is amenable to liver therapy. The course is nonfebrile. For some unknown reason, the anemia may at times become more active. Giblin observed about 20 cases during the twenty years from 1921 to 1941. Most of the patients were young men. In his opinion, malaria does not enter into the clinical picture as a cause, because most of the natives have acquired a full immunity to this disease.

The general subject of anemia in pregnancy is discussed by Roberts [32] who states that three main types are found: physiologic anemia, iron deficiency anemia and pernicious anemia of pregnancy. He reports 2 cases of the last type. He states that the macrocytic anemia induced by pregnancy is certainly not established as a separate entity. According to him, few cases have been investigated with thorough hematologic technic. He states that it is said to differ from addisonian pernicious anemia in that achlorhydria is rare and spontaneous recovery usually occurs after parturition. Changes in the cord are not seen. True pernicious anemia complicated by pregnancy is rare, because the age incidence is such either that patients have borne their children or that their fertility is so lowered by the anemia that they are incapable of bearing more. He reports, however, the case of 1 patient who had a child when she was 22 years of age. Her symptoms of pernicious anemia began when she was 33 years of age, and she conceived again some four years after her blood count had returned to normal. He states that judging by the dose of liver extract required to keep her in good health pregnancy did not seem to have affected her condition adversely. A second patient with pernicious anemia had also some evidence of iron deficiency. This patient had not conceived during the first eight years of her married life and did not do so until three years after her blood picture was first restored to normal. Her labor was complicated also by mitral stenosis, but there was no evidence of cardiac failure. As with the previous patient, the dose of liver extract required to keep her in good health remained the same after pregnancy.

The occurrence of severe megalocytic anemia in a 20 year old male vegetarian is reported by Cook.[32a] The patient's diet was adequate in calories, as indicated by his state of general good nutrition, but was obviously deficient in animal protein. The hemoglobin content was 35 per cent, the red blood cell count 1,400,000 per cubic millimeter and the white blood cell count 10,600 per cubic millimeter. The mean diameter of the erythrocytes was 8.2 microns. Hydrochloric acid was absent in the gastric secretions after injection of histamine during the stage of severe anemia but later appeared. There was a striking response to the injection of liver extract.

A fatal case of achrestic anemia in a 56 year old woman studied at necropsy is reported by Huse.[32b] The diagnosis was based on the finding of a macrocytic anemia which failed to respond to efficient anti-pernicious-anemia medication and a megaloblastic hyperplasia of the bone marrow. Achlorhydria was present, which was attributed to an associated chronic gastritis. No attempt was made to test for the presence or absence of the antianemic principle in the liver, but the author considered that sufficient evidence was present without this information to substantiate the diagnosis of achrestic anemia.

Treatment, Including Pernicious Anemia.—A comprehensive article on the treatment of the chronic anemias by Reznikoff [33] may be read with profit by any one coming in contact with patients who have anemia. Reference will be made to the treatment of the macrocytic anemias only. He warns that to treat anemia with "shot gun" therapy is usually uneconomical and often results in failure. Iron should be given only for iron deficiency states, liver therapy for macrocytic

31. Giblin, W. E.: Some Clinical Notes on Macrocytic Anaemia in New Guinea Natives, M. J. Australia **1**:89, 1944.

32. Roberts, G. F.: Pregnancy in Pernicious Anemia, St. Barth. Hosp. J. **48**:53, 1944.

32a. Cooke, R. T.: Megalocytic Anaemia in a Young Vegetarian, Brit. M. J. **1**:558, 1944.

32b. Huse, A. A.: Achrestic Anaemia with Achlorhydria, Brit. M. J. **1**:184, 1944.

33. Reznikoff, P.: Treatment of the Chronic Anemias, M. Clin. North America **28**:368, 1944.

anemia and transfusions to treat anoxia and as a palliative measure. According to this author, with whom we agree, unless a patient has a macrocytic anemia or one entirely or in part due to a lack of intrinsic or extrinsic factor, there is no justification for the use of liver extract. Furthermore, if there is no reticulocyte response in five to ten days or a conspicuous rise in the number of red blood cells within two or three weeks after the beginning of therapy, the continued use of liver therapy is not indicated. We are in agreement with his emphatic statement that the intramuscular injection of liver extract is the route of choice for administration and that only for a rare patient who is sensitive to parenteral treatment should oral therapy be considered. He recommends that the average patient with pernicious anemia receive 15 to 30 U. S. P. units of an accepted liver extract intramuscularly daily until the reticulocyte peak is reached — that is, for a week to ten days. After this, the frequency of the injections may be decreased to three times a week until the red blood cell count reaches 4,000,000 per cubic millimeter. He agrees that the maintenance dose varies rather widely; some patients may need only 15 units a month and a few need as much as 15 units a week. Infections, neurologic signs and symptoms and possibly arteriosclerosis may alter the amount of the maintenance dose. He warns that a patient who has paresthesia, diminished vibratory sense and other signs of neurologic involvement should receive more therapy than a subject free from these. He also advises that such patients should take large amounts of vitamin B for their peripheral neuritis.

Sippe [34] treated a large number of patients with nutritional macrocytic anemia whom he encountered in Mauritius. This condition was particularly common in members of the community who did not include beef flesh in their diet for religious reasons. The anemia occurred in both sexes and was most prevalent during the second and third decades. It was especially apt to appear in the latter half of pregnancy. In patients who also had malaria and splenomegaly, the disease was probably aggravated by the excessive destruction of normal and abnormal erythrocytes by the hypertrophied reticuloendothelial system. A number of patients with nutritional macrocytic anemia were successfully treated with yeast obtained locally as a waste product in the manufacture of alcohol by the fermentation of molasses. The potency of the material obtained from the distilling vats was due to the presence of autolyzed yeast, which contains one or more factors necessary for the normal maturation of red blood cells and in whose absence an anemia of the macrocytic type develops.

A scholarly discussion of the etiologic factors responsible for the production of pernicious anemia and of the bearing which spontaneous remissions may have on this subject is given by Bloomfield.[35] He contends that a study of the spontaneous remissions and other data which he presents supports the toxic hemolysis theory of pernicious anemia rather than the concept of deficiency of material necessary for the maturation of red blood cells. Evidence is cited to indicate that true spontaneous remissions actually occur and that they are not the result of inadvertent ingestion of antianemia materials. Furthermore, he contends that spontaneous remissions are not readily explained on the deficiency theory but are compatible with the theory of intermittent action of a toxic substance. He shows that transfused blood disappears during a relapse, whereas it is "held" during remission. Furthermore, he emphasizes that there are variations in the maintenance dose of effective antianemia material from time to time in the same patients and that they are difficult to explain on the basis of deficiency but are compatible with the toxic hemolysis theory. He also points out the interesting fact that many elderly people have a deficient gastric secretion and presumably an inadequate supply of Castle's intrinsic factor, yet they fail to acquire pernicious anemia. Furthermore, he points out that total gastrectomy is certainly not always followed by the development of pernicious anemia as one would anticipate if Castle's theory were entirely correct. Certainly his arguments are thought provoking and merit careful consideration by all persons interested in the disease.

Myers [36] summarizes his experience in dealing with 85 cases of pernicious anemia and discusses various diagnostic and therapeutic problems. He emphasizes that in 6 per cent of his patients with pernicious anemia carcinoma of the stomach developed and states that one might anticipate a much higher percentage since both conditions begin with gastric atrophy. He mentions, among other things, that gallbladder disease is not uncommonly associated with pernicious anemia,

34. Sippe, G. R.: Autolyzed Yeast in the Treatment of Nutritional Macrocytic Anemia, Brit. M. J. **1**:656, 1944.

35. Bloomfield, A. L.: The Spontaneous Remission of Pernicious Anemia: Its Bearing on the Nature of the Disease, Stanford M. Bull. **2**:5, 1944.

36. Myers, F.: Vagaries in Diagnosis and Treatment of Pernicious Anemia, Ohio M. J. **40**:635, 1944.

but one wonders whether there is an etiologic relation. It is stated that 4 of his patients had myxedema and that a combination of desiccated thyroid and anti-pernicious-anemia medication is required to bring these patients to normal. Intrigued by the occurrence of pernicious anemia in a husband and wife, he asks the question "Is pernicious anemia a dietetic or a marital failure?" It is his opinion that oral therapy is not as effective as parenteral and should never be recommended for patients with neurologic symptoms. He concludes that 84 per cent of his patients were improved with treatment, 2 per cent were unimproved and 14 per cent died. Changes in the spinal cord still present the greatest problem in the treatment of this disease, and the response to intensive therapy is still far from satisfactory. According to him, vitamin B complex and nicotinic acid are of doubtful value.

Important studies relating to the incidence and causes of relapses in pernicious anemia have been made by Schwartz and Legere.[37] Their report is based on the observations on 54 patients with 88 individual self-induced relapses brought about by discontinuance of anti-pernicious-anemia therapy, either immediately after release from the hospital or months or even years after a satisfactory maintenance dose had been established. All their patients were from an economic level below average and dependent in part for subsistence on various forms of financial aid. For the most part, their diets were suboptimal in animal proteins, vitamin B factors and vitamin C. It is obvious, therefore, that these observers were dealing with a type of patient who was most likely to have a relapse when therapy was inadequate. The patients who discontinued therapy returned in a state of relapse at intervals varying from two to thirty-eight months. About one third of them had relapses during the first six months, approximately another third in the next six months, about 24 per cent in the second year, 5 per cent in the third year and 1 per cent later. They were unable to correlate such factors as sex, age, race, total amount of liver administered, duration of treatment before discontinuance and average monthly dose with the "relapse period." Patients with pernicious anemia who require relatively small amounts of liver extract to maintain a normal blood level may have relapses in as short a time as two months after the therapy is omitted. Studies dealing with the "depot method" of administration of large amounts of liver extract at one time indicate that there is some storage of the liver principle when massive quantities are given, but this is not a quantitative storage. It is the opinion of these observers that the factor of relapse is a highly singular phenomenon which is remarkably inconstant, even in the same patient. They believe the "individual relapse period" is probably intimately linked with the quantitative secretion of the "intrinsic factor," the quantity of "extrinsic factor" and of other essential dietary factors and the storage of the "anti-pernicious-anemia principle" in the liver. This analysis probably does not tell the entire story, since there is no correlation between the "relapse time" and the average amount of liver necessary for maintenance. It is suggested that a cyclic change may take place in the glands of the stomach which secrete the intrinsic factor and that such changes may account for the variability of the relapses and of the individual liver requirements from time to time. They conclude that previous studies which have attempted to evaluate massive dose therapy and the storage of liver extract are inaccurate because sufficient cognizance is not taken of the highly individualized behavior of patients with pernicious anemia during remissions.

A summary concerning 80 living patients with pernicious anemia who have been under treatment for variable periods is presented by Hardgrove, Yunck, Zotter and Murphy.[38] There was a possible family history of anemia for 12.5 per cent of the patients. The majority of their patients, approximately two thirds, were derived from German, Polish and Irish stock, and 1 was a Negro woman. It is of interest to note that in 14 per cent of the patients the hair became dark after treatment. The correct diagnosis of pernicious anemia was made during the first year of illness for only 36.25 per cent. For 53.75 per cent the diagnosis was not made by the first physician consulted, and for 86 per cent it was not adequately established until hospitalization. As is true in most groups of patients with pernicious anemia, the most common initial symptoms were weakness and fatigue. Sore tongue occurred at the onset in 56 per cent, paresthesias in 71 per cent, disturbance in the gait in 41 per cent, disturbance of the bladder in 42.5 per cent and gastrointestinal complaints in 82.5 per cent. Heart disease of a degenerative type was present in 33.7 per cent. Satisfactory maintenance of the red blood cell count and body weight were obtained in 66 per cent of the patients by one in-

37. Schwartz, S. O., and Legere, H.: Relapses in Pernicious Anemia, J. A. M. A. **124**:637 (March 4) 1944.

38. Hardgrove, M.; Yunck, R.; Zotter, H., and Murphy, F.: Summary of Eighty Living Cases of Pernicious Anemia, Ann. Int. Med. **20**:806, 1944.

jection of 3 cc. of crude liver extract (15 units) every four weeks and in 11.5 per cent by one every three weeks. For individual patients more frequent injections were required. Allergic reactions to liver extract were prominent in this series, as they were reported to occur in 27.5 per cent of the patients and in 5 compelled a change to oral therapy. As is usual for patients receiving treatment for pernicious anemia, some had relapses. Nineteen patients in this group discontinued treatment for periods of three months to five years, but all subsequently resumed it. The time elapsing before severe relapse occurred varied greatly for different patients.

The normal serum level of cholesterol was determined by Nayar,[39] as was the level of the cholesterol in anemia and also the effect of cholesterol therapy in various types of anemia. He found the blood level of cholesterol in Indians to be lower than that in Europeans, as indicated by a maximum of 152, a minimum of 100 and a mean of 126 mg. per hundred cubic centimeters in nonpregnant natives of India. In pregnant women of India the maximum blood level of cholesterol is given as 247, the minimum as 112 and the mean as 179.5 mg. He observed that the blood cholesterol level is low in persons suffering from any type of anemia, irrespective of the variety. In some instances the blood cholesterol is reported to be as low as 66, 58 or 25 mg. per hundred cubic centimeters. In 1 instance it was 20 mg. These observations seem to be unbelievably low. It was not thought that the blood cholesterol level runs parallel with the red blood cell count or the hemoglobin concentration of the blood. Furthermore, he concludes that infections, bacterial, protozoal and helminthic, seem to lower still further the blood cholesterol level of anemic persons. The effect of cholesterol therapy on anemia is discussed. The patients were given intramuscular injections of 5 per cent solution of cholesterol in olive oil, 2 cc. daily or on alternate days. Various types of anemia were treated, but 40 patients out of the 51 studied presented a macrocytic hyperchromic blood picture; 5 were orthochromic and normocytic, and the remaining 6 were hypochromic and microcytic. Of the 45 patients with macrocytic hyperchromic and normocytic orthochromic anemia, 41 were pregnant and 4 were nonpregnant. He concluded that cholesterol did not take the place of liver in the treatment of patients with tropical macrocytic anemia but that the combination of cholesterol with liver therapy in treatment of the severely ill patients with macrocytic anemia of pregnancy might be better than liver alone. In treatment of tropical macrocytic anemia in nonpregnant patients, cholesterol supplements the hemopoietic action of iron to a certain extent, but even in such cases improvement is much more rapid with liver therapy. He states that the blood cholesterol level is low in all cases of severe anemia, irrespective of pregnancy.

Young and Bett[40] emphasize correctly the fact that a laboratory method for the determination of potency of liver extracts intended for the treatment of patients with pernicious anemia would be of great value. They review the method reported by Overbeek and his associates,[41] in which explants of bone marrow from normal guinea pigs are cultured in a solid medium of saline solution and heparinized plasma. In this medium, cells, which are chiefly leukocytes, migrate from the explants to form a reasonably clearcut zone of migration. According to them, the addition of an active liver extract is said to stimulate the migration. A modification of this method has been utilized by Young and Bett. They report their conclusions as follows: They are unable to confirm reports of a quantitative or qualitative relation between the occurrence of "a peak" in migration of cells from normal guinea pig bone marrow grown in the medium mentioned. According to them, peak migration does not take place consistently at any dilution from 1:100 to 1:300,000 of extracts of known anti-pernicious-anemia activity but occurs irregularly whether or not liver extract is present. Furthermore, they conclude that little if any added stimulation by purified extract occurs. There is no difference, therefore, which is sufficiently definite and which can be used as a basis of any methods of assay.

According to Davis and Allinson,[42] previous studies have shown that experimental polycythemia may be produced in dogs by the feeding of raw liver or by the injection of purified solution of liver and by the feeding of choline hydrochloride. The authors undertook an investiga-

39. Nayar, S.: Cholesterol and Anaemia, Indian M. Gaz. **77**:459, 1942.

40. Young, C. M., and Bett, H. D.: Bone Marrow Procedure for Assay of Liver Extracts for Anti-Pernicious Anemia Activity, J. Pharmacol. & Exper. Therap. **81**:248, 1944.

41. Overbeek, G. A.; Gaillard, P. J., and de Jongh, S. E.: Ein qualitatives und quantitatives Testverfahren für die Wirkung antianamischer Leberextrakte in vitro, Schweiz. med. Wchnschr. **68**:711, 1938. Gaillard, P. J.; Overbeek, G. A., and Yam, T. H.: Action of Anti-anemic Preparations on Bone Marrow in Vitro, Arch. internat. de pharmacodyn. et de thérap. **64**:33, 1940.

42. Davis, J. E., and Allinson, M. J. C.: The Presence of a Choline-Like Substance in Several Injectable Solutions of Liver, Proc. Soc. Exper. Biol. & Med. **54**: 266, 1943.

tion for the purpose of determining whether highly purified solutions of liver extract for parenteral use contain any choline or choline-like activity. After studying six injectable liver extracts, they concluded that each one contained choline or choline-like substances which on acetylation produced vasodepressor activity which was antagonized by atropine.

Sensitivity to Liver Extract.—A matter of increasing importance to all physicians who administer anti-pernicious-anemia medication is the occasional occurrence of various "reactions" to this type of treatment. The most comprehensive review dealing with this subject is one written by Kaufman, Farmer and Reich.[43] They record that since 1931 there have been thirty-five articles dealing with this subject, in which a total of 50 patients are reported as having experienced reactions from liver extract by injection. In addition, they report on 11 patients, 4 of which were seen personally by them and 7 whose detailed histories were provided by other physicians. While reactions to various types of anti-pernicious-anemia medication are not common, nevertheless they are observed in every large hematologic clinic and are likely to occur in the experience of all physicians who give liver extract intramuscularly. There have been a few reports of allergic reactions from the oral ingestion of liver, either raw or cooked, or of liver extract, but reactions most commonly occur when the medication is given intramuscularly. It may follow the use of almost every type of liver extract, including the European preparations. It is also known that when patients experience a reaction from one brand they are likely to have the same untoward effect from other preparations. To a certain extent, the amount of extract injected is of importance, but this is not always true. It is known that a reaction may occur locally after a test dose with as minute an amount as 0.1 cc. of a 1:1,000 dilution intracutaneously. On the other hand, it has been observed that a patient may have a reaction when 1 cc. of Reticulogen (liver extract with added thiamine hydrochloride) is given subcutaneously, whereas this effect did not follow the injection of 0.5 cc. given in the same manner. Reactions most commonly occur after the product has been well tolerated for weeks, months or even years, especially after a long interval between the injections. The authors recognize the remarkable and unexplained fact that although the patient may have the initial reaction after numerous injections it may disappear for no apparent reason and never occur again despite a continuation of the same type of medication. The suggestion is made that these reactions may be due occasionally to inadvertent intravenous injections. Sensitivity to liver extract may persist for a long period, even up to eight years, as in 1 patient. The authors state that of the 61 patients with reactions to liver extract reported on in the literature only 6 were known to have definite evidence of allergy; 13 showed no other allergic manifestations, and concerning the remainder no statement was made. The clinical manifestations of the reactions to liver extract are exceedingly diverse. The most frequently encountered is either urticaria alone or in association with other allergic symptoms, such as pain, edema, erythema and itching. On the other hand, the reactions may be as severe as angioneurotic edema evidenced by the characteristic features of asthma. In some instances the manifestations of typical anaphylactic shock appear, such as weakness, a rapid and weak pulse, vomiting, dyspnea and a pronounced fall in blood pressure. The authors state that almost the whole gamut of allergic manifestations have been described. They report that no fatalities have occurred, although we can state that in some cases the symptoms are so severe as to suggest the possibility of an imminent fatality and 1 fatal case has been observed in England.[44] Of interest are the results of the intracutaneous tests performed with various brands of liver extract which are reported in the literature. The total number of patients who have had allergic reactions from liver extract who were subsequently tested intracutaneously number 26, of whom 24 showed positive results of cutaneous tests. Of 11 patients studied by Kaufman and his associates, 8 showed positive reactions. It is generally agreed that in a large majority the reactions following the oral or parenteral administration of liver extract are undoubtedly related to allergy. This opinion is supported by the clinical picture, the positive results of intradermal tests and the occasionally reported presence of reagins and precipitins. It is of interest to note that if the patients are allergic to some substance in the liver extract it is through sensitivity to the organ and not to the species of animal. For example, if a patient reacts to beef liver, it is likely that swine or sheep liver will produce the same effect. It seems reasonable to assume, therefore, that the sensitivity is to some

43. Kaufman, R. E.; Farmer, L., and Reich, C.: Allergic Reactions to Liver Extract, Ann. Int. Med. **19**:768, 1943.

44. Morgans, C. C.: Intolerance to Liver Extract in Pernicious Anemia, Brit. M. J. **1**:613, 1943; Sensitivity to Liver, Letters and Answers, ibid. **2**:29, 1943.

substance in liver, irrespective of its biologic source. The immediate symptomatic treatment of allergic reactions to liver extract consists of the injection of epinephrine hydrochloride (1:1,000) in a dose of 0.3 to 0.5 cc. subcutaneously. If there is a local reaction, it should be treated with calamine lotion containing phenol. The simplest way to avoid reactions is to discontinue the parenteral use of liver extract and to give the patient oral anti-pernicious-anemia medication, consisting of either liver extract or powdered stomach. Although changing to oral preparations may be of value in avoiding reactions, it is generally agreed that this method of therapy is less efficacious than is the intramuscular. It has been recommended by Taylor and Higler [45] that histaminase may be used. They assert that results of intradermal tests with liver extract following the use of this preparation are definitely less pronounced. There is no conclusive proof, however, to indicate that the clinical reactions are reduced, and it does not seem feasible to administer histaminase constantly throughout the remainder of the period in which the patient is to take liver extracts, especially if he has pernicious anemia. It is suggested by Kaufman and his associates that a more feasible therapeutic agent for patients who react frequently might be histamine in gradually increasing doses. They also recommend that desensitization with gradually increasing doses of liver extract is an excellent method for use in treating those patients who react regularly. They suggest that the initial treatment be the subcutaneous injection of 0.1 cc. of a 1:10 dilution, the dose being increased by about 0.2 cc. every second or third day for about three weeks until the patient is receiving the full therapeutic dose, such as Lederle's liver extract, 3 cc., or Reticulogen, 0.5 to 1 cc. In their opinion it is important to keep this type of patient "desensitized" by administering the extract in small quantities at more frequent intervals than is customary, at least once a week. When giving liver parenterally to such patients one should have epinephrine hydrochloride and a sterile syringe and needle at hand for emergency use. They also concede that although the patients may improve, as indicated by a decreased frequency of their reactions, one must take into account the spontaneous loss of sensitivity which occasionally occurs in these patients.

45. Taylor, C. B., and Higler, D. W.: The Use of Histaminase by Mouth in Preventing Systemic Reactions to Parenteral Liver Extract, J. A. M. A. **117**: 1880 (Nov. 29) 1941.

It is stated by McSorley and Davidson [46] that of 16 patients with pernicious anemia admitted consecutively to their wards during the past five years, in 4, or 6.6 per cent, reactions subsequently developed after one to three years of maintenance by intramuscular liver extract therapy. Reactions are classified into two groups, namely, primary and secondary. The primary reactions they consider as not due to an acquired sensitivity but to an immediate response of the body to the parenteral injection of foreign material. These are more likely to occur when the preparation is given intramuscularly. Secondary reactions to oral, intravenous and intramuscular liver therapy have been described, and McSorley and Davidson believe they are undoubtedly of an allergic nature. They recognize that if a patient is sensitive to one brand of liver extract sensitivity to other products is also likely and hence the sensitivity is related to liver rather than to any species, as other investigators have thought. Although they appreciate the limitations of cutaneous reactions in relation to sensitivity to liver extract, they suggest that it is worth while to perform cutaneous tests, since it is found that in the majority of cases the degree of cutaneous reaction bears some relation to the severity of the general sensitization and of the reactions which result.

For the patients with mild reactions they believe it is permissible to attempt to control the reactions by injecting 3 minims (0.18 cc.) of a 1:1,000 solution of epinephrine hydrochloride concurrently with the liver preparation. For other patients who have mild reactions they state that good results may be obtained by reducing the quantity of the injection to one half or one fourth of the dose which produced the reaction and decreasing the periods between injections by a quarter or a half. In the treatment of the patients with severe reactions, however, it is recommended that the parenteral administration of liver be replaced by oral ingestion of whole liver extract or of preparations of stomach or that desensitization be carried out. The latter procedure is recommended as cheaper and more effective than oral therapy. They warn, however, that desensitization is a potentially dangerous procedure unless carried out under strict supervision by some one familiar with the dangers of anaphylactic reactions. They refer to the 1 fatality following an allergic reaction to liver therapy, which was reported by Morgans [44] in the *British Medical Journal* in 1943. Using the technic which they describe in detail, they were able to

46. McSorley, J. G., and Davidson, L. S. P.: Sensitivity to Liver Extract, Brit. M. J. **1**:714, 1944.

desensitize successfully 15 patients who had previously experienced severe reactions.

It is stated by Engelhardt and Derbes [47] that reactions to the intramuscular injections of liver extract are not so rare as is generally thought, for they have observed several instances in a relatively short period. Various types of reactions are discussed, and the classification of Tausk [48] is considered. He divided the reactions into three categories: (1) erythematous reactions, (2) those ascociated with a fall in blood pressure or histamine-like reactions and (3) truly allergic reactions. In addition, they describe local reactions to liver extract. The authors observed a histamine-like reaction characterized by a fall in blood pressure associated with nausea which persists for half an hour or more. The patient in whom this reaction occurred had no subsequent untoward effects from liver extract by injection. They describe truly allergic reactions as being of the local type with erythema and edema, and a severe generalized allergic reaction as being characterized by difficulty in breathing, tachycardia and loss of consciousness. They suggest that an ampule of epinephrine should be available and that the drug should be given in doses of 0.3 to 0.5 cc. if necessary and that the local type of allergic reaction may be avoided by alternating the site of the injection just as one does with insulin. The statement that a substitution of one commercial product for another brand will often result in control of the untoward symptoms is not in accord with our experience or with that of other investigators who have noted reactions to liver extract. Their opinion that desensitization may be attempted but is generally unsuccessful also is not in agreement with our experience and with that of others with regard to methods of controlling reactions to liver extract. They consider that many patients may tolerate oral liver extract therapy well whereas they are sensitive to the preparations for intramuscular injection, and such is the experience of most observers. They also recognize that a change in the animal source of the liver is not apt to solve the problem, since the allergic reaction is to the liver and not to the animal.

47. Engelhardt, H. T., and Derbes, V. J.: Allergy to Liver Extract, South. M. J. **37**:31, 1944.

48. Tausk, N.: Bireacties na insuiting van Leverextracten, Nederl. tijdscher. v. geneesk. **80**:749, 1936.

(*To be Continued*)

Book Reviews

Arterial Hypertension: Its Diagnosis and Treatment. By Irvine H. Page, M.D., and Arthur Curtis Corcoran, M.D. Price, $3.75. Pp. 352, with 14 figures. Chicago: The Year Book Publishers, Inc., 1945.

Of the several books recently published on arterial hypertension, this one best fulfils the requirements of a general practitioner. A comprehensive study of arterial hypertension is presented with a minimum of theoretic detail. In their approach to the problem, the authors aim to study the patient as a whole, rather than to concentrate on hypertension by itself. They develop this idea in a manner which shows that they understand hypertension, the natural history of the disease, the intricate mechanisms involved and the psychic as well as the somatic reactions of the patient.

The book is divided into five sections: Sections I and II take up the definition and classification of hypertension and some phases of the examination of the patient. Sections III and IV include studies of the circulation, particularly the renal and the coronary circulation, and a clinical study of the heart and the kidneys in essential hypertension. Treatment, including therapy with drugs, treatment with endocrine substances and surgical intervention, are considered in section V. The appendix consists of a classification and a study of toxemias of pregnancy.

The authors' concept of the pathogenesis of hypertension is based on the theory that there is an early functional or emotional type of hypertension, in which the circulatory system is well adjusted and evidences of cardiac, renal or cerebral disorders are lacking. The only renal change seems to be a constriction of the afferent arterioles. "This may be called the . . . neurogenic . . . type of hypertension. Later in the course of the disease, another stage develops, in which evidences of vascular disease of the kidney, of the heart and of the arteries become evident." In this phase, the clinical picture is typical of essential hypertension. A transitional stage is also described.

Regarding the nature of the early vascular changes in essential hypertension, they believe the earliest one consists of conversion of the renal blood flow from a pulsatile to a continuous type of flow, resulting in the liberation of an enzymatic protein, renin. This, in turn, is responsible for the vasoconstriction of essential hypertension.

The proper approach to the diagnosis is taken up in a clear and simple manner. Special tests of renal function are briefly described, but the most useful ones are taken up in much greater detail. The tests recommended as most practical are: (1) measurement of proteinuria, (2) counts of the urinary sediment, (3) determination of urinary concentrating power and (4) determination of urea clearance.

A study of congestive heart failure, its cause, its course and its treatment, is excellently presented and is one of the highlights of the book.

In the discussion of treatment, thiocyanate is given first place. Kidney extract and vitamin A are discussed. Treatment by surgical measures is considered, and the effects of nephrectomy on hypertensive persons is given particular notice.

The book is written in a characteristic and easy style. Altogether, it is an interesting as well as a useful and authoritative monograph on the subject of arterial hypertension.

Penicillin and Other Antibiotic Agents. By Wallace E. Herrell, M.D. Price, $5. Pp. 348, with 45 illustrations. Philadelphia: W. B. Saunders Company, 1945.

With a new and rapidly moving subject, it is always a question at what point one is justified in summarizing current knowledge in book form. Dr. Herrell's monograph will always be a landmark in the history of antibiotics, if for no other reason than for the excellent chapters dealing with the discovery and development of these substances, the analysis of the literature and the classification of priorities. The general physician will perhaps be most interested in the discussions of technic of preparation and administration of penicillin and of the results of treatment in various conditions. The material is extensive and well presented, although much will have to be revised in the light of future (and indeed current) work, especially the matter of time-dose relation. The reviewer feels that the continuous intravenous method of administration will, except in rare instances, be replaced by intermittent intramuscular injections or by some other more effective method. It seems also that some of the doses recommended for severe sepsis are rather small. Little is said about bacterial endocarditis, and that not too encouraging, although good results are being reported now with large doses of penicillin. Finally, the discussion of syphilis will require much extension and amplification after more cases have been followed for a few years. The book is admirably printed and illustrated, and the bibliographies are thorough. The final chapters on antibiotics other than penicillin, such as tyrothricin, will be of great value in orienting the physician in a complicated subject.

Microbial Antagonisms and Antibiotic Substances. By Selman A. Waksman, Professor of Microbiology, Rutgers University, and Microbiologist, New Jersey Agricultural Experiment Station. Price, $3.75. New York: Commonwealth Fund, 1945.

Years of study and research in microbiology resulting in an intimate understanding of the subject have prepared the author to write this opportune book. Scientists have been aware of the interrelations of microorganisms for many years; recently an awakening to the possibilities of the practical application of these antagonistic relations has decidedly accelerated interest and investigation. The book describes and discusses the teeming microscopic plant and animal population of soil, water basins and human and animal wastes. It treats of their complicated interrelations, especially the antagonistic, the mechanisms of these reactions and the antibiotic substances produced and the utilization of antagonistic micro-organisms in the control of disease in human beings, animals and plants. Since more detailed studies have been made on the production, nature and utilization of penicillin, it is natural that special attention is focused on this agent, though the many

substances possessing bacteriostatic and fungistatic properties are given due consideration. The author has successfully accomplished the difficult portrayal of a rapidly moving scene.

Trauma in Internal Diseases. By Rudolf A. Stern, M.D., assistant attending physician, City Hospital, New York. Price, $6.75. Pp. xxiv + 575. New York: Grune & Stratton, Inc., 1945.

This book has an interesting history. There was printed in 1899 in Breslau a volume called "Ueber traumatische Entstehung innerer Krankheiten." Its author was Dr. Richard Stern, and it was a pioneer work in the field of traumatic medicine. It achieved success; a second edition appeared in 1907 and a third edition in 1929. The third edition, however, was pretty much a new book under an old title, put together by Rudolf Stern, who was the son of the original author.

This book might be termed the first American edition of Dr. Rudolf Stern's book, or possibly the fourth edition of his father's; for it is clearly modeled on the latest German edition, and much of it is a translation. By way of rejuvenation, certain new features have been added, and the bibliography has been brought up to date. On the whole, it gives a readable account of the European viewpoint toward trauma in medicine.

Biological Symposia, Volume XI, Aging and Degenerative Diseases. Edited by Robert A. Moore. Price, $3. Pp. 242. Lancaster, Pa.: The Jacques Cattell Press, 1945.

This is the age of symposiums, conferences and panels, and, according to the preface, "This volume contains the papers presented at a symposium in St. Louis, March 24th and 25th, 1944, under the joint sponsorship of the Research Unit of the St. Louis City Infirmary and the Washington University School of Medicine."

The papers all deal with some phase of the process of aging, but they make no claim to a systematic coverage of the subject, nor do they show any particular correlation. Some are reflective and semiphilosophic—meditations, if you will, *de senectute;* others report concrete results of experimental work, such as the interesting contribution of Saxton on nutrition and growth and their influence on longevity in rats. The volume is well printed and illustrated. There is no index.

Military Medical Manuals — Manual of Clinical Mycology. Prepared under the auspices of the Division of Medical Sciences of the National Research Council. Flexible cloth. Price, $3.50. Pp. 348, with 148 illustrations. Philadelphia: W. B. Saunders Company, 1944.

This book, like its predecessors, is a compact, readable and authoritative work on a subject that is not too well known. The subject is adequately dealt with from the bacteriologic, from the dermatologic and from the medical standpoint. Even surgeons might read the book with profit. It is remarkable how much information concerning molds and yeasts has been packed into this small space. There is a section dealing with the proper components of the various lotions, ointments and paints that may be prescribed in the treatment of these infections.

The book should be popular.

The Examination of Reflexes. By Robert Wartenberg, M.D. Price, $2.50. Pp. 222, with 6 diagrams. Chicago: The Year Book Publishers, Inc., 1945.

This concise little book lists and describes the methods of eliciting the innumerable reflexes used in clinical practice, discusses their significance and critically reviews the literature. The four hundred and sixty-five articles in the literature to which reference is made give an idea of the comprehensiveness of this monograph, which will be invaluable to the neurologist and the internist. The author, because of his original work in the field, seems specially qualified to discuss the subject.

Poet Physicians; An Anthology of Medical Poetry Written by Physicians. Compiled by Mary Lou McDonough. Price, $5. Pp. 210. Springfield, Ill.: Charles C Thomas, Publisher, 1945.

In this anthology of medical poetry written by physicians, some of the poems are good, some indifferent and some bad, but such variations in quality would be expected in any anthology. The good poems outnumber the poor, and some of the former have become almost classic in our poetic literature. The poems are numerous. It is surprising how prolific have been the doctors who are poets. Adding to the value of this anthology is a short sketch of the life of the authors whose poems are published and whose dates range from 699 A.D. to the present time.

News and Comment

GENERAL NEWS

MISSISSIPPI VALLEY MEDICAL SOCIETY

The Eleventh Annual Meeting of the Mississippi Valley Medical Society will be held Sept. 25 to 27, 1946, at the Hotel Jefferson, St. Louis.

The Mississippi Valley Medical Society is resuming its annual Essay Contest and in 1946 will offer a cash prize of $100, a gold medal and a certificate of award for the best unpublished essay on any subject of general medical interest (including medical economics) and practical value to the general practitioner of medicine. Certificates of merit may also be granted to the physicians whose essays are rated second and third best. Contestants must be members of the American Medical Association and residents of the United States. Contributions must not exceed 5,000 words, must be typewritten in English in manuscript form, and five copies must be submitted not later than May 1, 1946. Further details may be secured from Harold Swanberg, M.D., Secretary, Mississippi Valley Medical Society, 209-224 W. C. U. Building, Quincy, Ill.